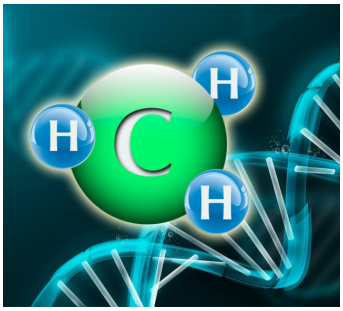
Methylation Puzzle Demystified



Rajko Bisevac ND, ABAAHP, FAARFM
purelifehealth@yahoo.com
630-846-1400

1

THE LATEST FAD

- Explosive rise in Genetic Testing

The motivation behind testing?

- What is my ancestry?
- What are my mutations?

2

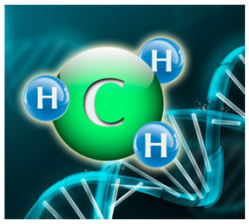
Genetic polymorphisms (SNP's) CLINICAL RELEVANCE

BEN LYNCH ND:

- "The majority of SNPs have no effect on the body at all. None. They could be in regions of the gene that don't impact the genetic function at all. It doesn't affect the shape, it doesn't affect the reading of the gene, doesn't affect the switching on or off of the gene."
- "A lot of people will get their genetic report and they're like, "Oh I have all these SNPs!" The question is, "Is that particular SNP clinically relevant?" There is another clinically relevant SNP, like MTHFR…677 is very relevant."

3

What is Methylation?



- Methylation is the process of adding a methyl group (CH3) to a molecule.
- This process occurs in every cell and tissue in the body and is the second most common biochemical process that occurs in the body.
- When a methyl group is added to a protein, it changes how that protein reacts to other substances

4

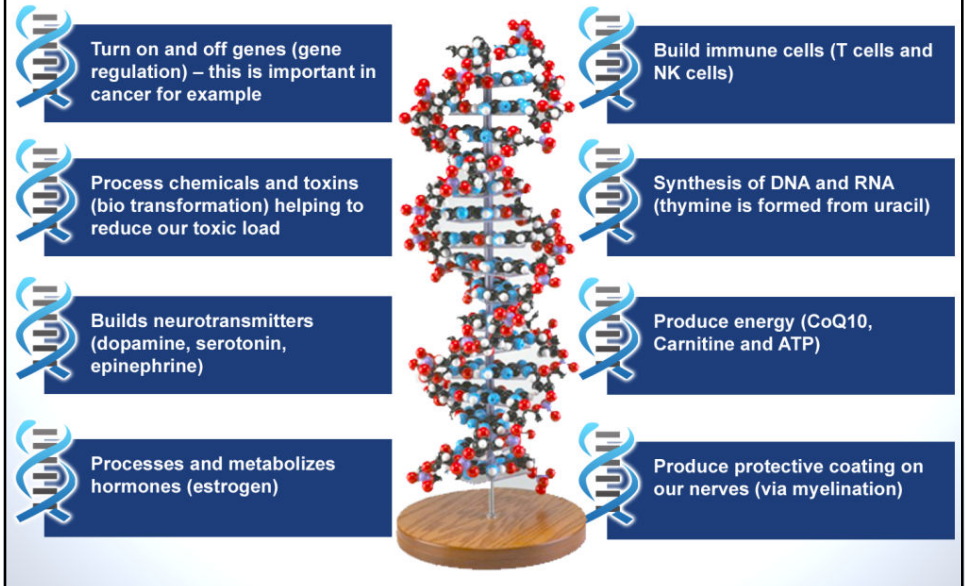
SYSTEMS AFFECTED

Methylation impacts reactions in the body that regulate the activity of various systems:

- Cardiovascular
- Neurological
- Reproductive
- Detoxification

5

KEY FUNCTIONS OF METHYLATION

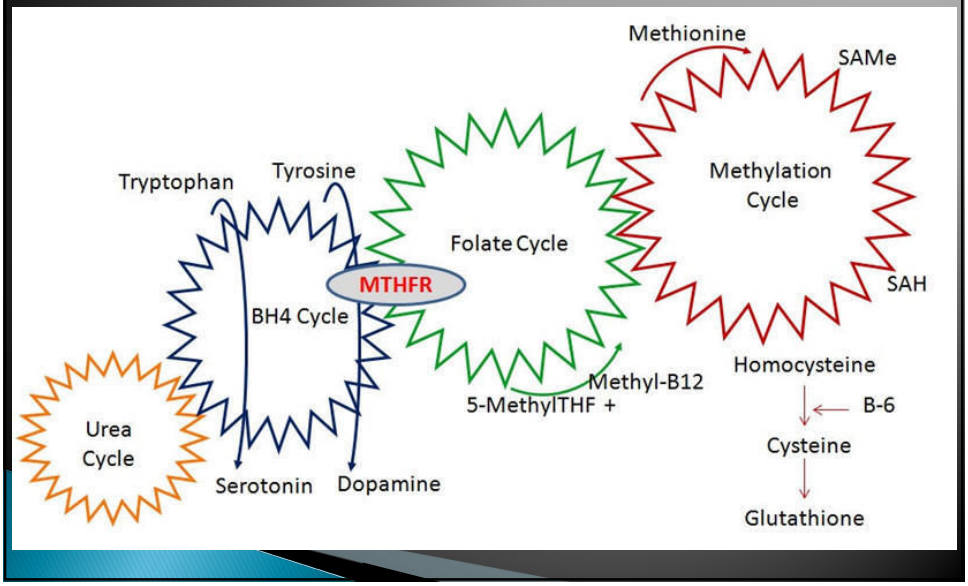


6

Swiss Clock

7

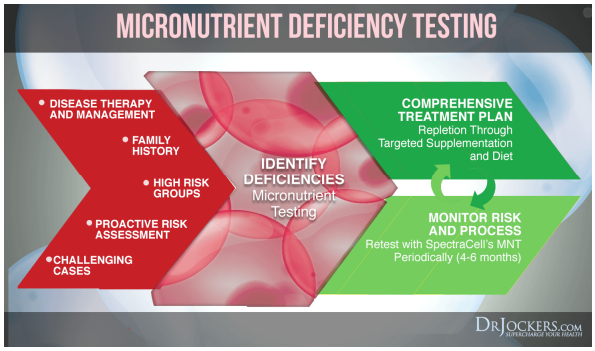
Overview of Cycles



8

Where do I start?

1. Evaluate the Patient
2. Symptoms?
3. Micronutrient Analysis and Genetic Analysis



9

What can influence Methylation?

1) ENZYMES
2) COFACTORS: Vitamins, minerals. Key nutrients: Mg, B2, B6, folate, B12, niacin
3) Rx: Oral contraceptives, NSAIDs, antacids
4) TOXINS, heavy metal exposure, chronic infections, alcohol, stress
5) MICROBIOME
6) GENETIC POLYMORPHISMS
7) EPIGENETICS

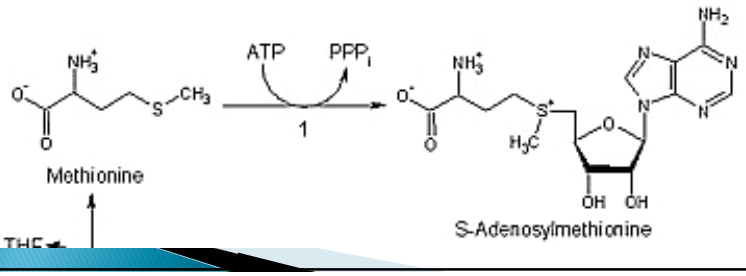
10

1) ENZYMES

11

How does methylation happen?

- Methionine, a sulfur-containing AA that enters the body through dietary proteins, has a methyl group attached to its sulfur atom.
- It becomes activated by ATP to form S-Adenosylmethionine or SAMe.



12

How does methylation happen?

- SAMe is the body's universal methyl donor.
- SAMe readily gives away its methyl group for the body to perform necessary functions.
- SAMe is also a precursor to the transsulfuration pathway, which leads to glutathione synthesis.
- However, the production of SAMe relies upon active folate (5-MTHF) and also B6, B2, B12.

13

- Oxidative stress slows the folate cycle, which impairs the body's ability to produce SAMe.
- Glutathione can help!
- Glutathione's job is to get rid of hydrogen peroxide in the body. If there is too much H2O2, it can block key enzymes needed for methylation, and H2O2 can shut down the cardiovascular and neurotransmitter systems.
- Glutathione carries B12 throughout the body and supports methionine synthase.

14

- Lungs store glutathione:
  - Kids who have lung issues have a depletion of glutathione.
- Too much glutathione can increase sulfites.
  - Sulfites can increase asthma.
  - Too many sulfites deplete B1.
  - If someone is sensitive to sulfites, Molybdenum helps.

15

Exercise-induced Asthma

- 40% of our ATP is used AT REST to pump Mg and K into the cell
- Adenosine inhibits the methylation cycle
- As you exercise and use up more ATP, adenosine levels go up from the breakdown of ATP into its components.
- As adenosine levels go up, SAH levels go up and SAMe goes down. Since SAMe is needed to break down histamine, histamine levels go up. This is exercise-induced asthma.
- Athletes need mitochondrial and methylation support.

16

MTHFR and Histamine

- MTHFR helps make SAMe;
- SAMe is a cofactor to help break down histamine
- Histamine needed in bell-shaped curve
  - Too little histamine can result in not enough stomach acid, slow gut motility and constipation

17

Diamine Oxidase (DAO) and Histamine Intolerance

- Diamine oxidase (DAO) is an enzyme that your body makes to break down histamine from foods.
- Without enough DAO enzyme, histamine intolerance can occur.
- Foods high in histamine:

Wine, beer, cheese, fermented foods, nuts, milk, soybeans, mushrooms, chocolate, shellfish, eggs, oily fish, citrus fruits

18

Diamine Oxidase (DAO) and Histamine Intolerance

- Histamine intolerance is different from allergies in that it's not linked to a specific food and does not involve immune cell reactions.
- The body also makes histamine. An imbalance between ingested histamine, the histamine released from our cells, and the ability to breakdown histamine leads to a buildup of histamine in the blood.
- Symptoms: migraines, redness and itching, nasal congestion, bloating, gas, stomach pain, nausea and vomiting, constipation, hives, dizziness

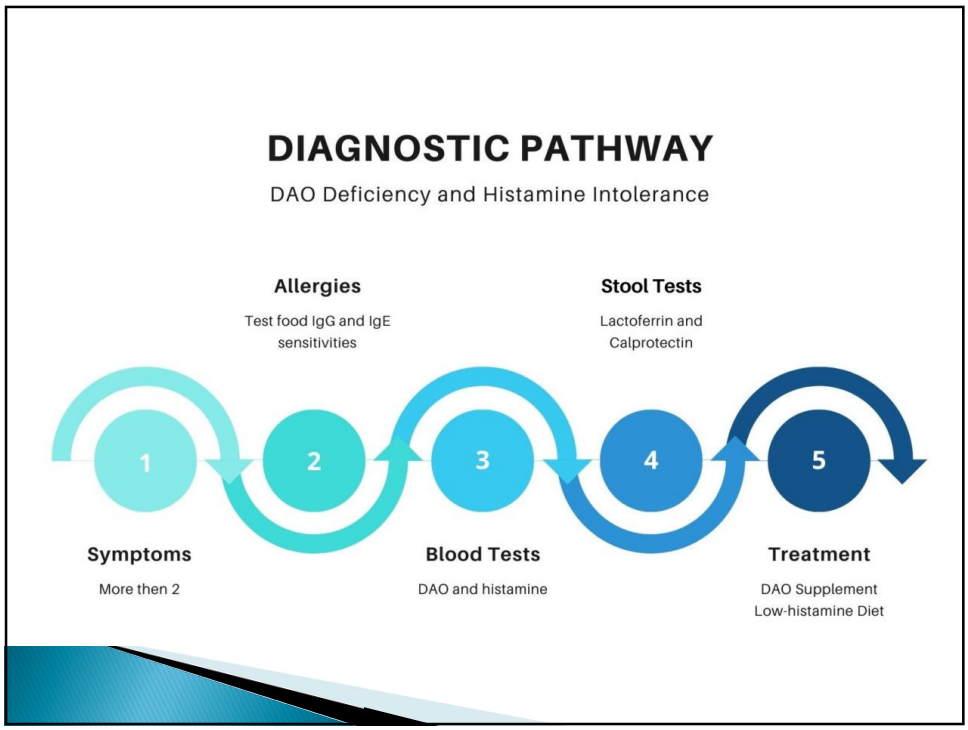
https://doi.org/10.3390/biom10081181
https://doi.org/10.1093/ajcn/85.5.1185
https://doi.org/10.1007/s10068-019-00627-3

19

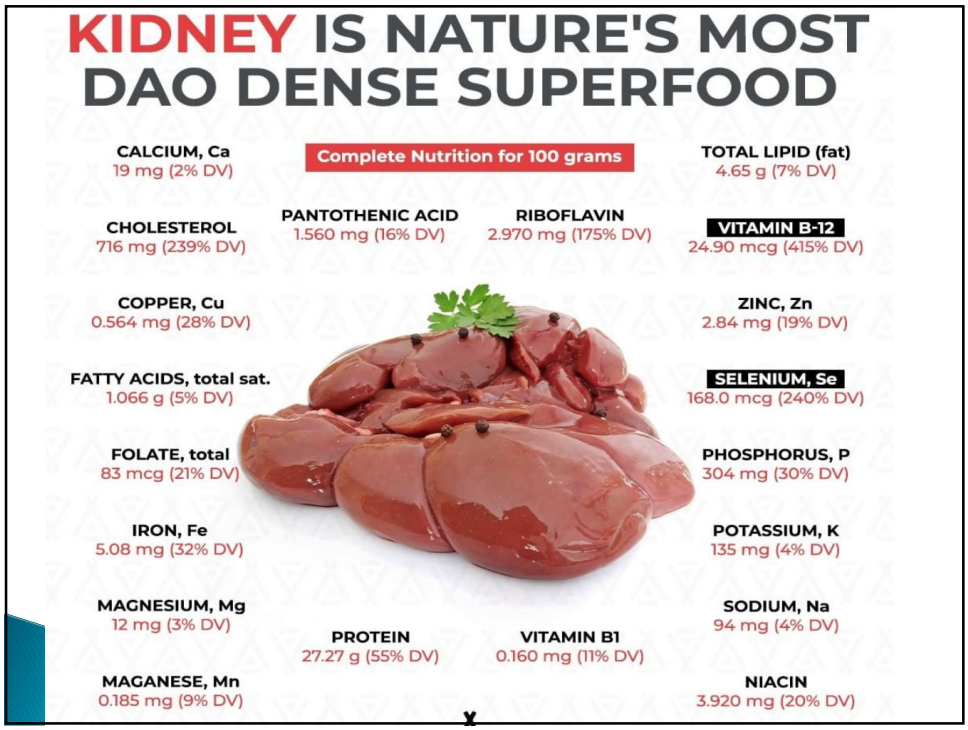
Tests for DAO Deficiency and Histamine Excess

LABORATORY	QUEST DIAGNOSTICS	LABCORP	PRECISION POINT DIAGNOSTICS
Diamine Oxidase (DAO)			>42. ng/mL
Plasma Histamine	<1.8 ng/mL	0.3-1.0 ng/mL	<1.2 ng/mL
Total Immunoglobuline E (IgE)	<114 kU/L	6-495 IU/mL	

20


DIAGNOSTIC PATHWAY
DAO Deficiency and Histamine Intolerance
Allergies
Test food IgG and IgE sensitivities
Stool Tests
Lactoferrin and Calprotectin
1
2
3
4
5
Symptoms
More then 2
Blood Tests
DAO and histamine
Treatment
DAO Supplement
Low-histamine Diet

21

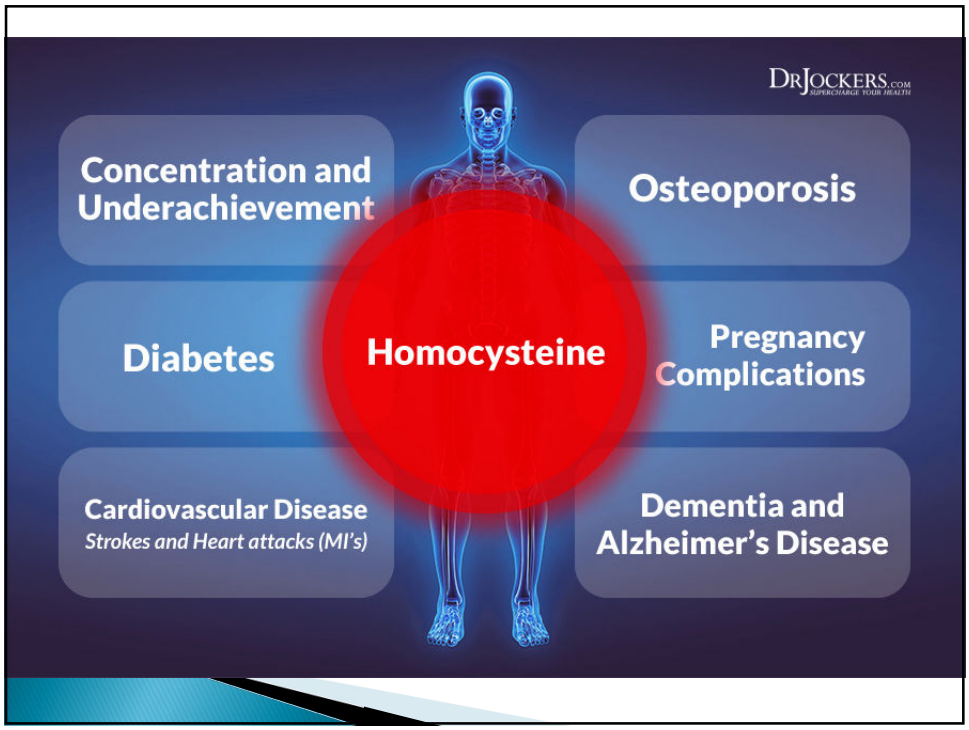

KIDNEY IS NATURE'S MOST DAO DENSE SUPERFOOD
Complete Nutrition for 100 grams
CALCIUM, Ca
19 mg (2% DV)
TOTAL LIPID (fat)
4.65 g (7% DV)
CHOLESTEROL
716 mg (239% DV)
PANTOTHENIC ACID
1.560 mg (16% DV)
RIBOFLAVIN
2.970 mg (175% DV)
VITAMIN B-12
24.90 mcg (415% DV)
COPPER, Cu
0.564 mg (28% DV)
ZINC, Zn
2.84 mg (19% DV)
FATTY ACIDS, total sat.
1.066 g (5% DV)
SELENIUM, Se
168.0 mcg (240% DV)
FOLATE, total
83 mcg (21% DV)
PHOSPHORUS, P
304 mg (30% DV)
IRON, Fe
5.08 mg (32% DV)
POTASSIUM, K
135 mg (4% DV)
MAGNESIUM, Mg
12 mg (3% DV)
SODIUM, Na
94 mg (4% DV)
PROTEIN
27.27 g (55% DV)
VITAMIN B1
0.160 mg (11% DV)
MAGANESE, Mn
0.185 mg (9% DV)
NIACIN
3.920 mg (20% DV)

22

Homocysteine

- Excess homocysteine limits the bioavailability of nitric oxide, increases oxidative stress, alters the elastic properties of the vascular wall, and damages the endothelium of blood cells
- Homocysteine excess → to a buildup of SAH
- SAH buildup inhibits COMT → impaired catecholamine and catechol estrogen metabolism
- SAH buildup inhibits DNMT → accelerated aging and malignancy

23

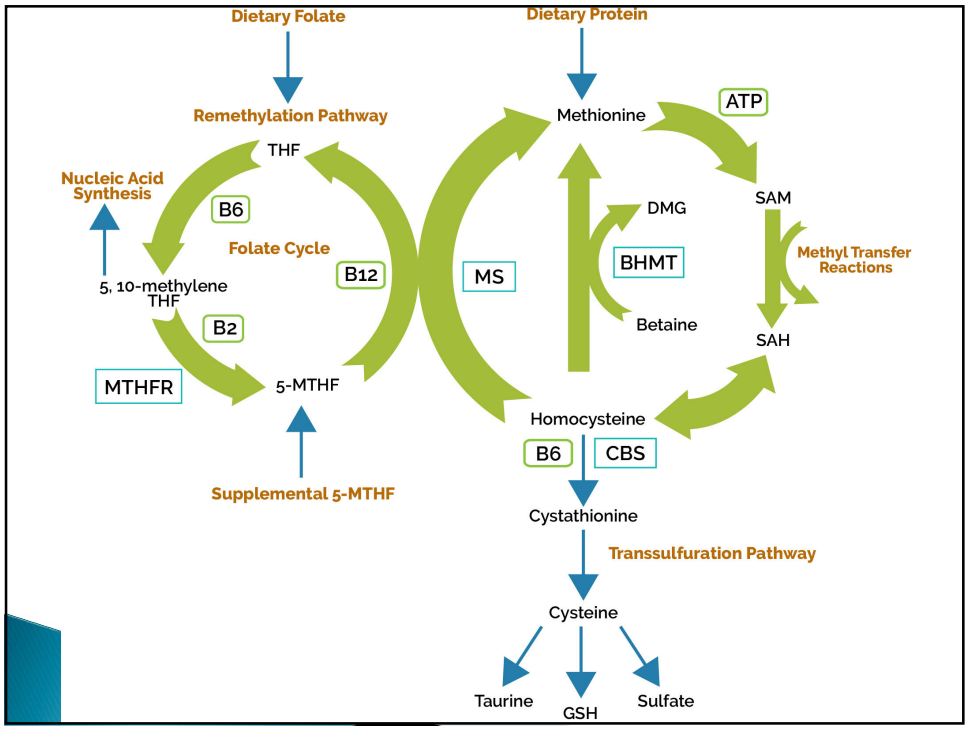


24

Glutathione

- When there is a deficiency in sulfur-containing amino acids, glutathione levels suffer.
- Dietary excess of sulfur AA's are readily oxidized to sulfate, excreted in urine, or stored in the form of glutathione.
- Cysteine and methionine are not stored in the body.
- Taking methionine and sulfur helps to increase glutathione.

25



26

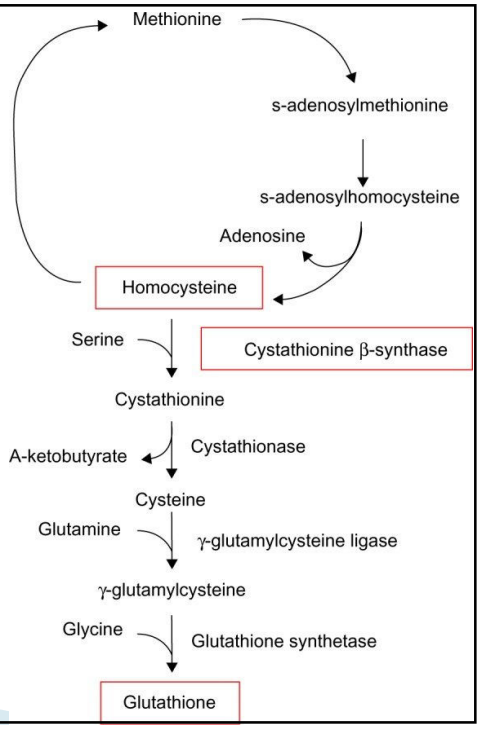
METHYLATION END PRODUCTS

- When methylation is inhibited and the body is not producing enough SAMe, a number of molecules down the cycle cannot be produced efficiently:

❖ Glutathione	❖ Melatonin
❖ Cysteine	❖ Serotonin
❖ Taurine	❖ Norepinephrine
❖ CoQ10	❖ Epinephrine
❖ Nitric Oxide	❖ L-Carnitine

27

- When SAMe gives away its methyl group, it is converted to SAH (S-adenosyl homocysteine), which then converts to homocysteine.
- Homocysteine can take two pathways, either converting back to methionine or entering the transsulfuration pathway, which leads to glutathione production.



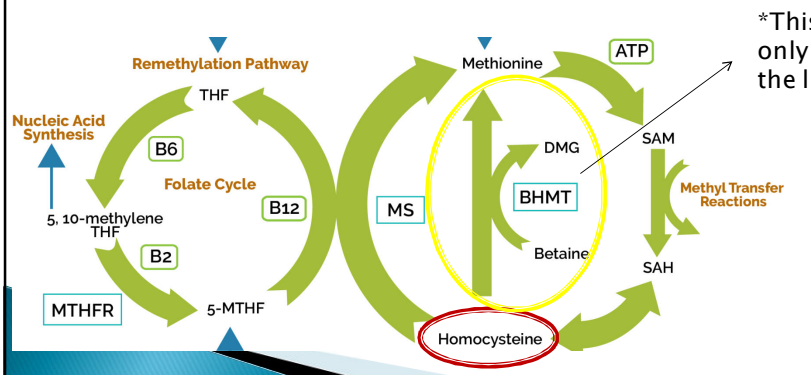
28

Glutathione – Master Antioxidant

- Antioxidant and regenerator of vitamin E and carotenoids, as well as an intracellular enzyme.
- One of its key functions is to reduce oxidative stress and remove toxins.
- Lowered levels of glutathione are linked to
  - oxidative stress
  - toxin and heavy metal build-up
  - immune dysfunction
  - thyroid problems
  - slow brain processing speed
  - low red and white blood cell counts
  - hair loss
  - poor digestion and absorption

29

- It is estimated that 60% of homocysteine is metabolized in the liver by transsulfuration.
- If homocysteine does not enter the transsulfuration pathway, it can be converted back to methionine in 2 different ways with the addition of a methyl group.



*This pathway only occurs in the liver.

30

SAMe supplementation

- SAMe is commonly used for depression.
- There is documented evidence that it helps to restore liver function from chronic liver disease.
- Likewise, it can prevent/reverse liver toxicity brought on by Rx such as Tylenol or steroids.
  - https://www.sciencedirect.com/science/article/pii/S0168827812004096
  - https://ajcn.nutrition.org/content/76/5/1183S.long
  - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4027041/

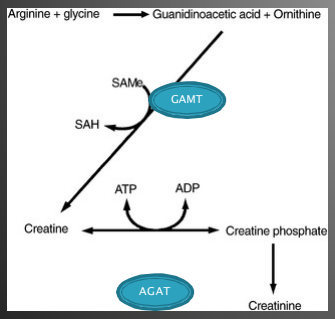
31

SAMe supplementation

- Studies show that SAMe improves joint health in osteoarthritis comparably to NSAIDs without the side effects.
  - https://pubmed.ncbi.nlm.nih.gov/3318441
  - https://pubmed.ncbi.nlm.nih.gov/12436324
  - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC387830/
  - https://pubmed.ncbi.nlm.nih.gov/12019049
  - https://pubmed.ncbi.nlm.nih.gov/3318442
- SAMe has also shown to reduce symptoms of fibromyalgia.
  - https://pubmed.ncbi.nlm.nih.gov/3318438
  - https://pubmed.ncbi.nlm.nih.gov/3318438
  - https://pubmed.ncbi.nlm.nih.gov/17602996

32

SAMe from Methylation Cycle



70% of SAMe from methylation cycle goes to Creatine Synthesis. Creatine helps to maintain a continuous supply of energy to muscles.

33

SAMe supplementation

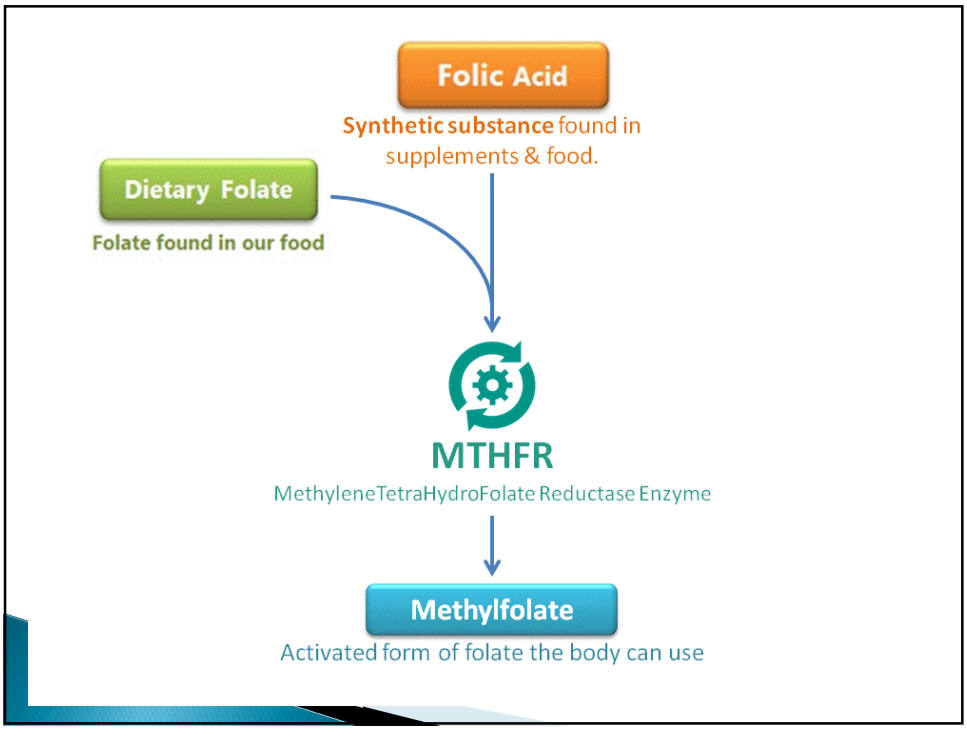
- If you give SAMe to a person, and they feel worse:
  1. Most likely, their methylation was inhibited
  2. The little neurotransmitters they have were used up
- Methylation blocks:
  - Oxidative stress
  - Inflammation
  - Poor gut health
  - Toxins / metals
  - Alcohol and sugar
  - Adrenal stress

34

What is MTHFR and why is it critical for Methylation?

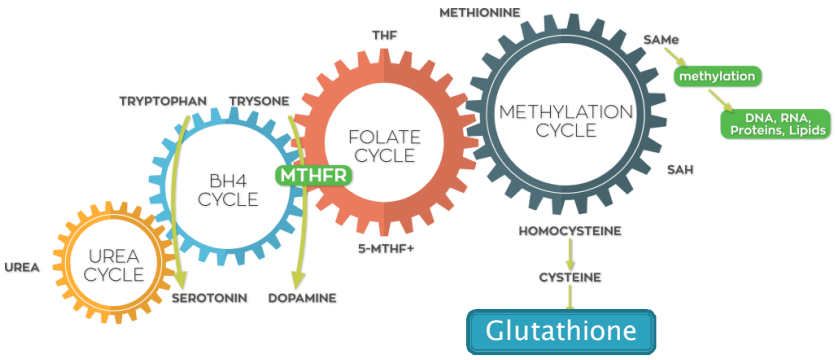
- Methylenetetrahydrofolate reductase
- Enzyme responsible for synthesizing the circulating form of folate; metabolizes folic acid/folate into 5-MTHF
  - 5-MTHF is needed for homocysteine regulation
  - (homocysteine can be toxic)
  - 5-MTHF combined with homocysteine facilitates liver detoxification processes
- Essential for body to function properly
- Affects more than 20 processes

35



36

Glutathione – Master Antioxidant



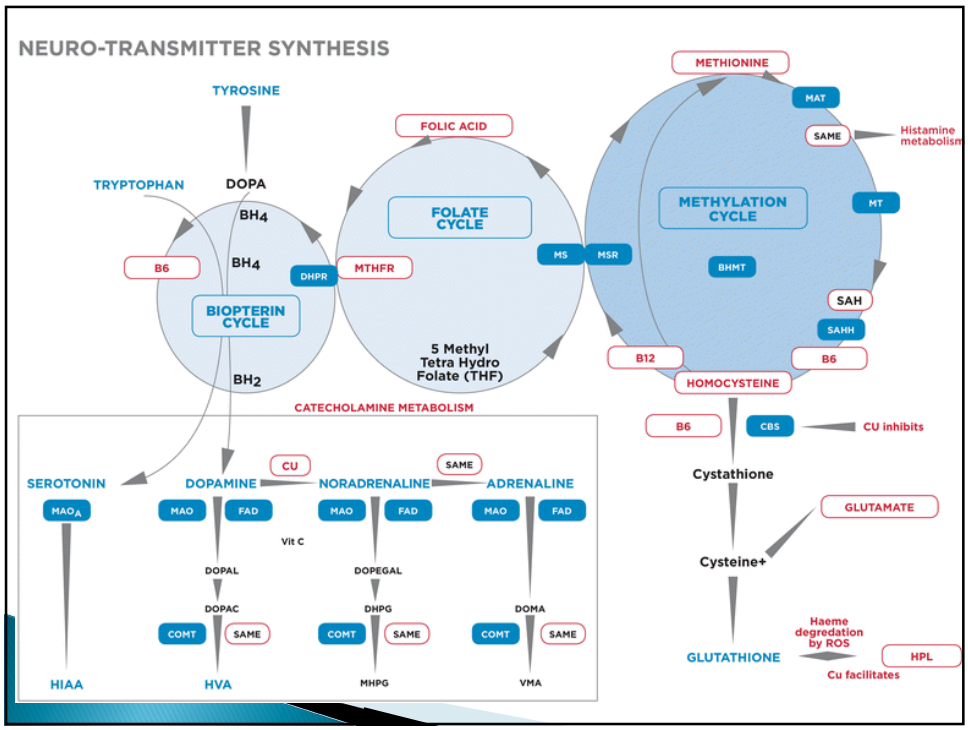
- MTHFR mutation can lead to less than optimal detoxification with up to 80% reduced capacity

37

5-MTHF functions

1. 5-MTHF regulates levels of the cofactor biopterin, which is required for the synthesis of neurotransmitters.
2. 5-MTHF is used to convert homocysteine to methionine, thus regulating homocysteine levels
3. 5-MTHF is ultimately responsible for the regulation of gene expression, as it is used in the methionine cycle to produce the major methyl group donor, SAMe.

38



39

MTHFR and BH4 pathway

- 5-MTHF affects the synthesis of neurotransmitters by regulating levels of the cofactor biopterin
- Biopterin is required for the synthesis of monoamines such as dopamine and norepinephrine

40

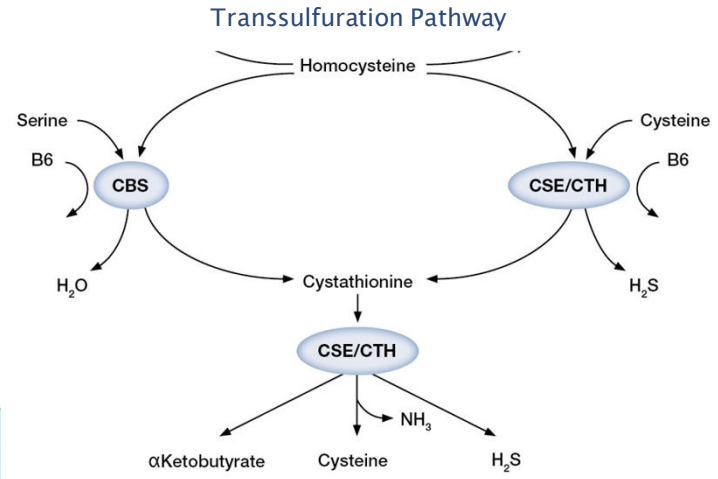
CBS and SUOX (Transsulfuration)

- We may need to address these gene mutations first before starting an MTHFR protocol...
- As with any of the SNPs in the methylation cycle, you can't just treat the SNP. You must look at the big picture and see what the other factors are that may have impact on the enzyme in question.

41

CBS: Cystathione-β-synthase

- Converts homocysteine into cystathionine



42

CBS deficiency

- Glutathione boosting supplements such as MSM, TMG, NAC and silymarin can cause negative side effects if there is a CBS enzyme deficiency, because sulfur is not being broken down properly
- CBS deficiency is associated with low dopamine, low serotonin, cardiovascular risks, and multiple chemical sensitivities
- CBS mutation can cause difficulty in the breakdown of ammonia

43

RECOGNITION of CBS UP REGUALTIONS

Low Homocysteine
- Normal Homocysteine with MTHFR and MTRR abnormalities

Sickest functionally ill patients:
- Autistic spectrum disorders
- Multiple chemical sensitivities
- Fibromyalgia and chronic fatigue

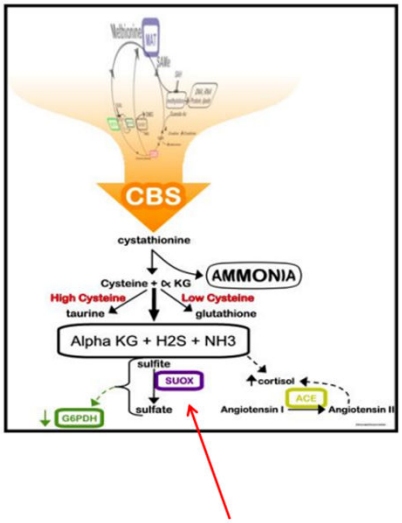
Sensitivities to:
- Alcohol and high sulfite/sulfate foods/supplements/pharmaceuticals
- MSG
- DMSA and DMPS
- B vitamins
- Post-prandial arrhythmia

Lab tip offs:
- Low molybdenum, serine, and B6
- Elevated taurine, cysteine, glutamate, and ammonia
- Elevated tyrosine, phenylalanine, and tryptophan with
- Low dopamine, norepinephrine, or serotonin or low HVA and VMA

44

CBS support

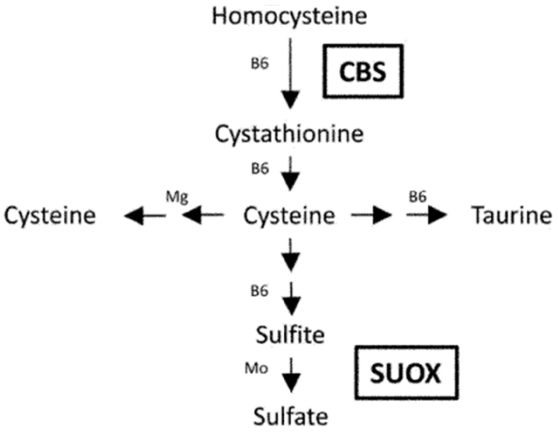
- ✓ Decrease sulfur foods
- ✓ Support SUOX
- ✓ Molybdenum
- ✓ Minimize dairy
- ✓ Hydroxycobalamin
- ✓ Boron
- ✓ Vitamin E
- ✓ Monitor Sulfite/Sulfate



45

SUOX: sulfite oxidase

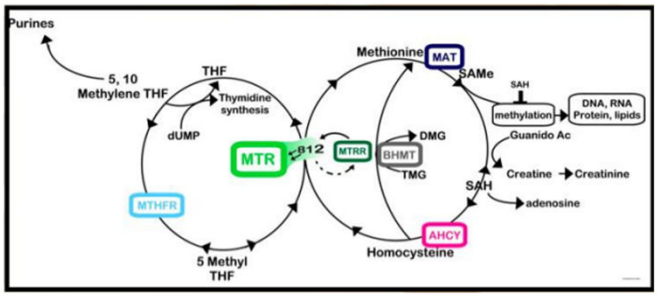
- This enzyme catalyzes the oxidation of sulfite to sulfate, the final reaction in the oxidative degradation of the sulfur amino acids cysteine and methionine.



46

MTR – Methionine Synthase

5-Methyl Folate + Homocysteine ⟶ Methionine + THF
Methyl-B12 (from MTRR)



Function Dependent on Methyl-Folate and Methyl-B12

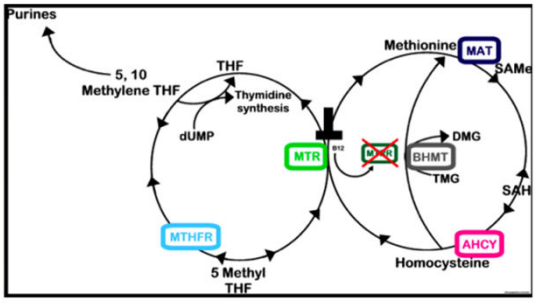
MTR sensitive to Mercury and Alcohol

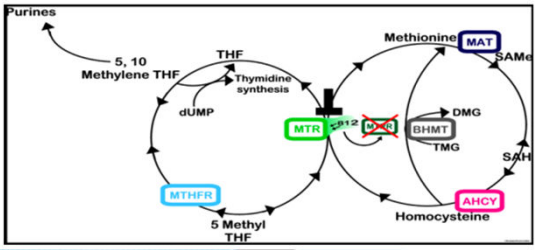
Inhibited by SAMe and Oxidative Stress

47

METHIONINE SYNTHASE REDUCTASE (MTRR)

B12 + CH3 (SAMe) ⟶ Methyl-B12





MTRR abnormalities
are all
Down Regulations

Treatment:
- High Dose B12
- Methyl-B12

Caveats:
- CBS/BHMT
- COMT

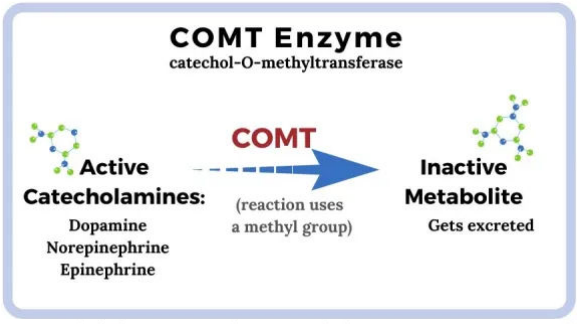
MTR Up Regulation
MTRR Down Regulation

→ Pronounced
Methyl-B12 Deficiency

48

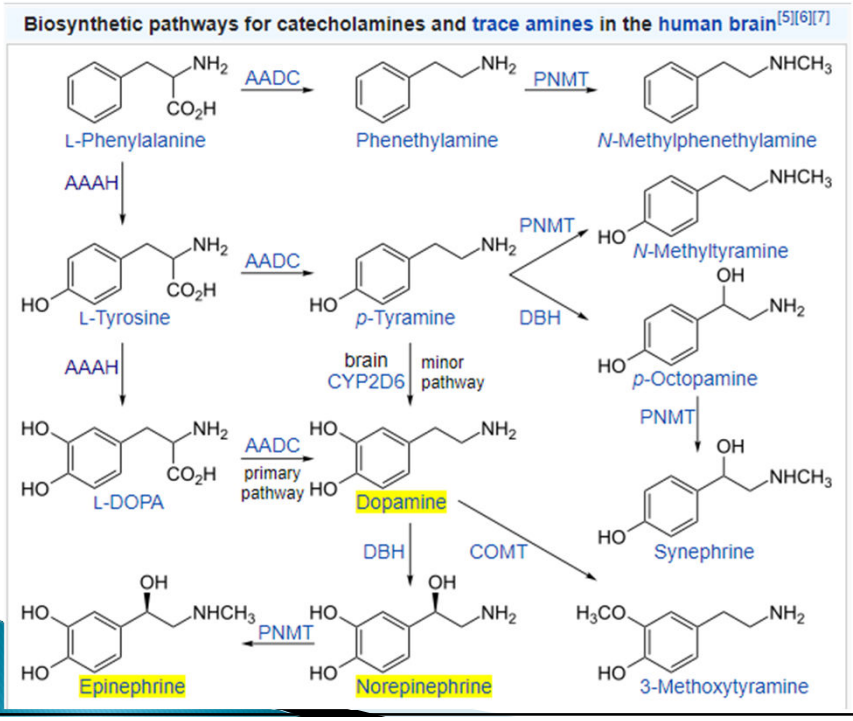
COMT – Catecholamine-*O*-Methyl Transferase

- COMT adds a methyl group from SAMe to catecholamines to inactivate and excrete them.
- If catecholamines accumulate, cardiovascular symptoms result.
- COMT also converts estrogen to be excreted.



Low folate → High homocysteine → High SAH → COMT Inhibition

49



50

Coffee and CV Risk

Coffee provides bioflavonoids and caffeine
Caffeine → Norepinephrine and epinephrine → Methylated by COMT → SAH
Caffeic acid → Methylated by COMT → SAH
Caffeine inhibits adenosine metabolism → SAH

- If COMT is functional and/or SAH/homocysteine are low, this is not a major issue.
- If COMT is dysfunctional and SAH is high, then this can be a major issue.

51

SAMe Methyl Transfer Reactions

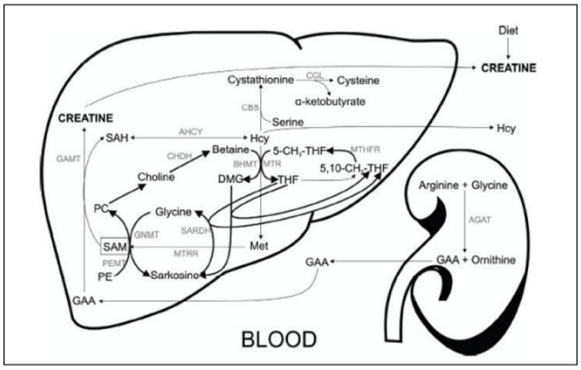
DNA methyl transferases	Alters DNA Transcription
Synthetic Reactions	Generation of Carnitine
PRMT Protein methyl transferases	Alters Enzyme Activity (PGC-1α → PPARα → FA Oxidation)
COMT Catechol-O-methyl transferase	Inactivates Catecholamines Methylates 2-OH and 4-OH Estrogens Metabolizes Bioflavanoids
PEMT Phosphatidylethanolamine N-methyl transferase	Generation of Phosphatidylcholine
GAMT Guanidinoacetate N-methyl transferase	Generation of Creatine
GNMT Glycine-N-methyl transferase	SAMe → 5,10-MethyleneTHF

52

GUANIDINOACETATE N-METHYL TRANSFERASE (GAMT)

$$\text{GAA} + \text{SAMe} \xrightarrow{\text{GAMT}} \text{Creatine} + \text{SAH}$$

GAMT
Stimulated by GAA
Not inhibited by Creatine



53

1. Reduce neuro-excito-toxicity

- Symptom
  - Agitation
  - Inflammation
  - Pain
  - Anxiety
  - Brain fog
- Symptom/Enzyme
  - Sulfites (SUOX)
  - Ammonia (CBS)
  - Glutamate (GAD)
  - Super oxide/Peroxynitrite (SOD/GST)
  - Membrane Instability (PEMT)
  - Histamine (DAO, HNMT)

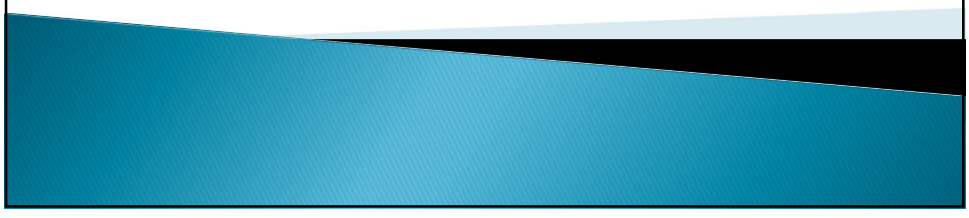
54

Micronutriets & Methylation

ENZYME	COFACTOR/PROMOTER
SUOX	B1, Molybdenum
CBS	B6, Cysteine
SOD / GST	Mn, Zn, Cu, Se
MTR	B12, Zinc, 5-MTHF
MTRR	B2
MTHFR	B2
COMT	Mg, SAMe
MAO-A	B2
GAD	Mg, B6
PEMT	Choline
BHMT	Omega DHA, Choline

55

2) COFACTORS

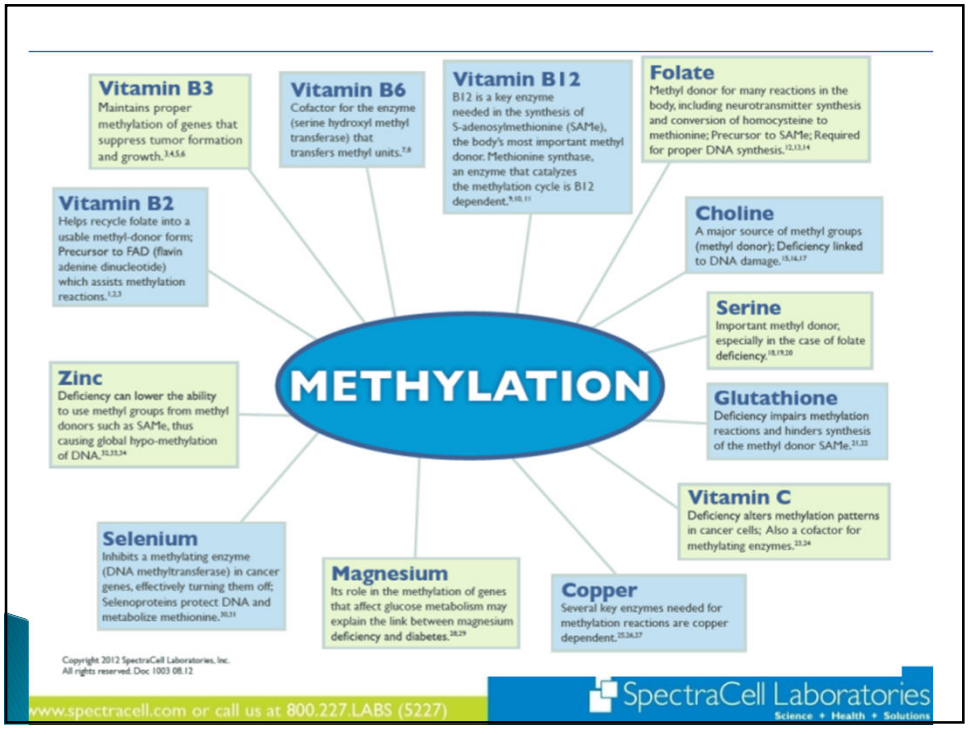


56

COFACTORS

- B2
- B3 (Niacin)
- B12
- FOLATE
- CHOLINE
- C
- Cu
- SERINE
- MAGNESIUM
- SELENIUM
- ZINC
- GLUTATHIONE

57



58

BH4 – Tetrahydrobiopterin

- AKA sapropterin (INN)
- Cofactor of the enzymes:
  - phenylalanine 4-hydroxylase (phenylal. to tyrosine)
  - tyrosine 3-hydroxylase (tyrosine to l-DOPA)
  - tryptophan 5-hydroxylase (tryptophan to 5-HTP)
- Used in the biosynthesis of neurotransmitters:
  - Serotonin (5-HT), melatonin, dopamine, norepinephrine, epinephrine
- Cofactor for the production of nitric oxide

59

5-MTHF supplementation caveats

- CBS upregulation and/or BHMT downregulation – Watch Sulfate status
- COMT downregulation – watch for mood swings

- These must be resolved also:
  - Other vitamin, mineral, AA imbalances
  - Problems with methylation
  - Excess folic acid toxicity, heavy metal toxicity
  - Immune system imbalances
  - Problems with energy production
  - Homocysteine, hormone and neurotransmitter imbalances

60

Differentiating B12, folate, B6 deficiency

Homocysteine ⇧ with no other result	Either B12, B9, B6, or methyl donors
MMA ⇧ with Hcy and FIGLU normal	B12
Homocysteine ⇧ with normal MMA	B6 or folate
Both Homocysteine ⇧ and MMA ⇧	B6 and possible methyl donors
Homocysteine ⇧, Normal MMA/FIGLU	B6 and possible methyl donors
HCY, MMA, and FIGLU all ⇧	B6, B12, B9, and methyl donors

- ✓ If MTHFR SNP, need 5-MTHF
- ✓ If MTRR SNP, need methylcobalamin
- ✓ B6 as pyridoxal-5 phosphate (P-5-P) – more effective form
- ✓ B2 (riboflavin) needed if MTHFR 677 SNP

61

Methylation Adaptogens

- Several natural compounds can also act as adaptogens in DNA methylation by both maintaining proper methylation status and regulating improper methylation activity. Furthermore, methylation adaptogens can help prevent abnormal DNA methylation which can cause a variety of health issues.
- Several methylation adaptogens include; curcumin, betanin, anthocyanins, quercetin, rosmarinic acid, lycopene, and sulforaphane.

62

Functional Markers of Impaired Methylation

- Low serum folate
- Low serum B12
- High serum MMA (methylmalonic acid)
- High serum homocysteine
- Low RBC folate
- High urine MMA
- High urine FIGLU (formimino-glutamate)

63

B12

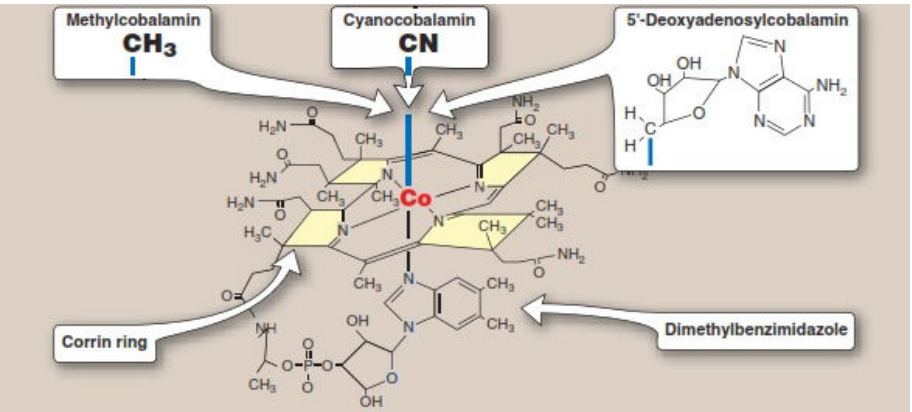
- B12 is synthesized only by microorganisms; it is not present in plants.
- Animals obtain B12 from their natural bacterial flora or by eating foods derived from animals: milk, eggs, liver, fish, meat.
- B12 deficiency is rarely a result of an absence from the diet (except for vegans/vegetarians.)
- It is much more common to see a deficiency resulting from a failure to absorb B12.

64

- The molecular state of B12 introduced to the body impacts the efficiency by which it is absorbed.
- B12 bound to protein in foods must undergo a separation reaction before it can be absorbed in the small intestine.
- Supplemental or free forms of B12 do not undergo this separation reaction.

65

Different Forms of B12



66

Mechanism of B12 Absorption

- If vitamin B12 is ingested in its free (or nonprotein bound form), it will bind to a carrier protein known as R-binders or transcobalamin I that is secreted by both the salivary glands in the oropharynx and the gastric mucosal cells within the stomach.
- If the vitamin B12 is ingested in its protein bound form, it must first undergo a proteolytic cleavage in the stomach or duodenum where it will bind to an R-binder and enter into the duodenum for further cleavage.
- Upon entry into the second segment of the duodenum, the pancreas will secrete additional protease which will then degrade the R-binders holding onto the vitamin B12. It is at this point that vitamin B12 will bind to or complex with intrinsic factor for the remainder of its journey to the ileum of the small intestine for absorption.

67

Active vs Passive B12 Intake

- Intrinsic factor (IF) is a special transport molecule produced by the parietal cells in the stomach.
- There is a limited number of IF receptors, which limits the amount of B12 intake via active intake: 1.5-2µg maximum. This process also requires calcium.
- B12 can also be absorbed passively when taken in high doses – between 200-1000µg. Only about 1% is absorbed!
- Unlike other water-soluble nutrients, B12 can be stored in the body for years.

68

B12 deficiency risks

- following a vegetarian or vegan diet
- being over 50 years old
- gastrointestinal disorders, including Crohn's disease and celiac disease
- surgery on the digestive tract, such as weight loss surgery or bowel resection
- metformin and acid-reducing medications
- specific genetic mutations, such as MTHFR, MTRR, and CBS
- regular consumption of alcoholic beverages

69

B12 TESTS

- Vitamin B12
- There are several markers of B12 status. A serum B12 can provide a rough estimate of B12 status, but there are many other indicators of B12 status:
- Vitamin B12 (serum)*
- Conventional range: 200-800
- Optimal range: 500-1000
- *It is well-established in the literature that people with B12 levels between 200-350 have distinct B12 deficiency symptoms:
- Alzheimer's, dementia or memory loss
- Depression, anxiety, bipolar, psychosis
- ADD/ADHD
- Fatigue
- Numbness or tingling
- Nerve pain

70

B12 TESTS

- Methylmalonic acid (MMA)- this is a very sensitive test and will reveal a true B12 deficiency if high. If your serum B12 was "normal" but you still have signs of B-12 deficiency, ask your doctor to order the MMA test
- MCV is a measure of the average volume of your red blood cells. When MCV is high, this is indicative of B12 or folate deficiency. When MCV is low, this is indicative of Iron deficiency. This is part of a routine CBC test.
- Conventional range: 80-100
- Optimal range: 83-90

71

Possible Tests

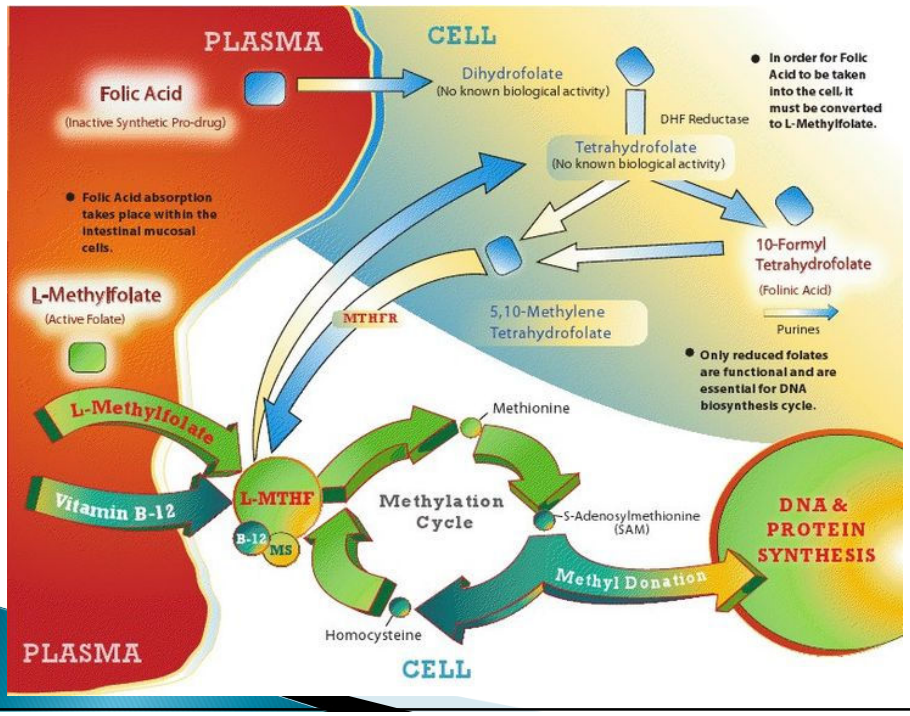
URINE	N-methyl nicotinamide (NMN) Methylmalonic acid (MNA) Formiminoglutamic acid (FIGLU) Total sulphate Free sulphate	Thio-sulphate Thio-cyanate Kryptopyrrole Sulphite
WHOLE BLOOD	Histamine Folinic acid	Riboflavin Niacin
RBC	Glutamate oxalo-transminase (GOT) Glutathione peroxidase (GP) Glutathione reductase (GR)	
PLASMA	THF 5-methyl THF 5-formyl THF 10-formyl THF Homocysteine Cysteine Taurine Cystathionine Glycine Methionine Serine	FAD FNM Total sulphate Free sulphate Adenosine Inosine Uridine NADPH TMG DMG
PLASMA & RBC	Glutathione Oxidized glutathione Folic acid Pyridoxal-5-phosphate	SAM SAH Vitamin B12 Vitamin B6

72

Methylation follows U-shaped curve

- Too much is not a good thing!
- Sometimes people feel good for a short time after supplementing, then start feeling worse.
- Several folate-requiring enzymes are INHIBITED by excess substrate; https://doi.org/10.1074/jbc.M410818200
  - Modest increases will activate the enzymes;
  - Large concentrations can inhibit them.
- Folate deficiency as well as over-supplementation can damage DNA. https://doi.org/10.1002/mnfr.201500819
- Increased folate can mask B12 deficiency. https://doi.org/10.3390/nu8020068
- Excess folate can cause nerve damage with B12 deficiency. https://doi.org/10.3945/ajcn.116.139030

73



74

Synthetic Folic Acid

- Folic acid is used to "fortify" many foods to prevent neural tube defects and to lower plasma homocysteine.
- FA is also found in many supplements.
- Large populations in the US have an unprecedented high FA intake.
- Unmetabolized folic acid in plasma was associated with reduced natural killer cell cytotoxicity in postmenopausal women.

https://doi.org/10.1093/jn/136.1.189

- Plausible link between too much folic acid and nervous tissue damage associated with autism.

https://doi.org/10.1016/j.mehy.2011.03.013

75

Synthetic Folic Acid

1. Folic acid is a synthetic compound that has NO physiological function until converted to dihydrofolate by dihydrofolate reductase (DHFR)
2. The DHFR enzyme breaks down folic acid much slower than naturally occurring folates which causes a build up of folic acid.
3. Folic acid has a stronger attraction to the folate receptors, blocking them from pulling natural folates into the cell for metabolic processes (our natural folates like leafy greens are essential for our folate levels)
4. In order for folic acid to be utilized, additional vitamin C, niacin and vitamin B12 are needed.

76

Folinic Acid = 5-formyltetrahydrofolate

1. Folinic Acid is the active metabolite of folic acid
2. Folinic acid has direct physiological functions that help create the building blocks of DNA
3. Folinic acid bypasses the DHFR enzyme in the folate cycle, making it an ideal supplementation strategy if you have a DHFR mutation that reduces your ability to metabolize folates and folic acid

77

Upper Limits on B Vitamins

- B vitamins are water soluble, so most are safe even at very high doses, as any excess is excreted in urine.
- B Vitamins with upper limits:
  - Folate/Folic acid – 1mg
  - Niacin
  - Vitamin B6

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4772032/

78

Folate and Pregnancy

- A baby's neural tube develops within the first 28 days of pregnancy. Folate is crucial to prevent neural tube defects.
- Folate also prevents certain heart abnormalities, cleft lip, cleft palate.
- Folate lowers the risk of developing anemia, miscarriage, preterm delivery and low birth weight.

https://doi.org/10.1093/advances/nmaa017

79

Note on Labeling

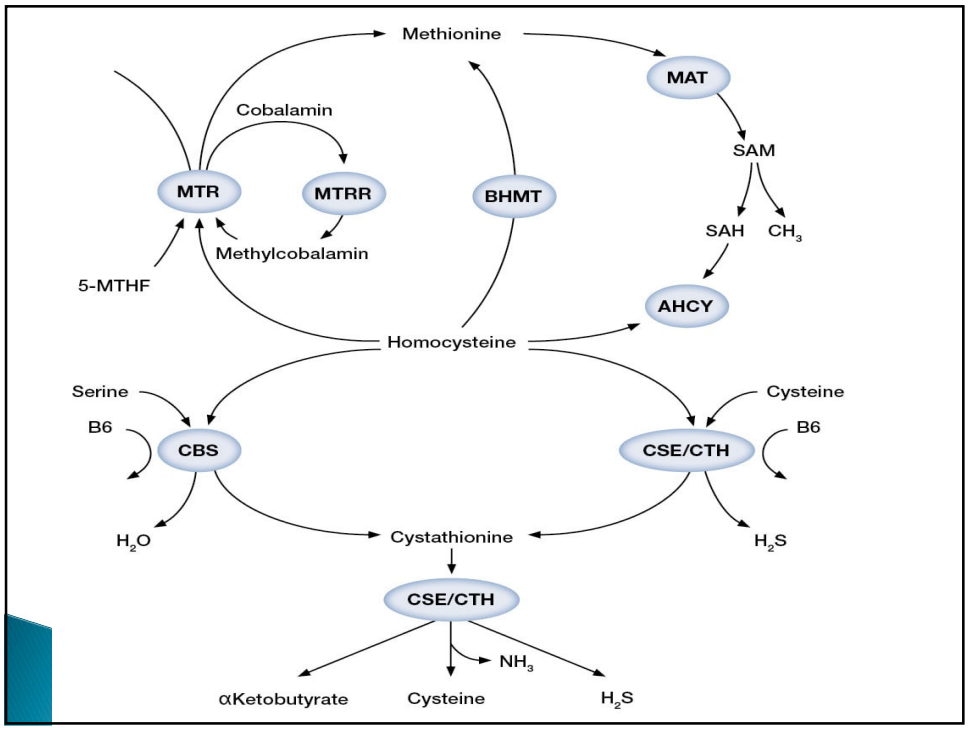
- FDA laws require folate labeled as µg DFE
- DFE = Dietary Folate Equivalents
- 1 µg DFE = 0.6 µg folic acid

80

Choline in Pregnancy

- Choline is the primary methyl donor backup to methylfolate.
- Pregnant women are 70% deficient in choline.
- Choline feeds into the transmethylation cycle that directly takes homocysteine back to methionine.
- 85% of methylation reactions occur in the liver, and the liver needs choline.
- SAMe and choline during pregnancy can reverse liver issues.

81



82

3) Rx Interactions

83

Drugs affecting Methylation

Drug	Hcy	Mechanism
Fibrates	↑	Decrease in GFR; depletes TMG
Cholestyramine	↑	Blunts folate and B12 absorption
Niacin	↑	Uses methyl groups; blocks B6 synthesis
Metformin	↑	Blocks B12 absorption
Insulin	↓	↑ MTHFR > ↓ CBS
Estradiol	↓ or ↑	↑ PEMT and depletes B6
Testosterone	↑	↑ Need for creatine
Methotrexate	↑	Blocks DHFR
Dilantin	↑	↓ MTHFR and MTR
Carbamazepine	↑	Folate depletion
Cyclosporin	↑	Decrease GFR and ↓ MTHFR
Levodopa	↑	Generation of SAH
NAC	↓	Thiol-disulfide exchange

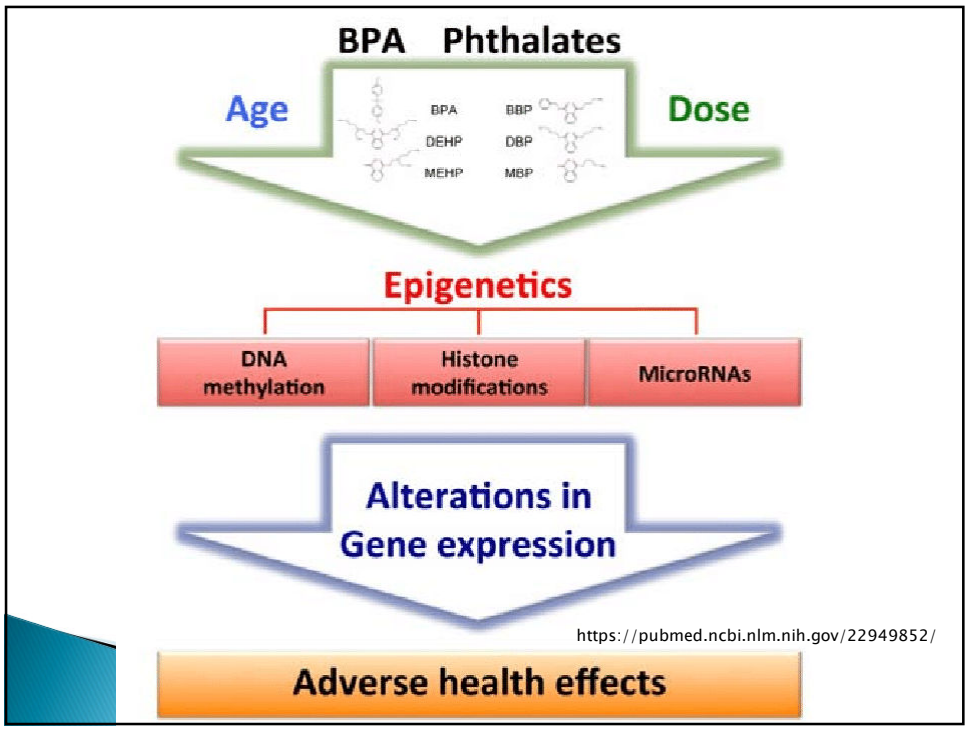
84

Drug	Hcy	Mechanism
PPIs and H_2 Blockers	↑	Blocks B12 absorption
OCPs	↑	↓ B12, B6, folate, riboflavin, Vit C, & Zn
Alcohol	↑	↓ MTR; compromises folate metabolism
Mercury	↑	↓ MTR
Lead	↑	Enzyme dysfunction
Aluminum	↑	Enzyme dysfunction
Cadmium	↑	Enzyme dysfunction
Organic Pollutants	↑	Enzyme dysfunction
Diuretics	↑	Lowers GFR; depletes B Vits
Spironolactone	No Δ	No effect
β-Blockers	↓	Uncertain mechanism

85

4) TOXINS

86


BPA Phthalates
Age
Dose
BPA
DEHP
MEHP
BBP
DBP
MBP
Epigenetics
DNA methylation
Histone modifications
MicroRNAs
Alterations in Gene expression
https://pubmed.ncbi.nlm.nih.gov/22949852/
Adverse health effects

87


5) MICROBIOME

88

Gut Bacteria have Methylation Cycles Also!

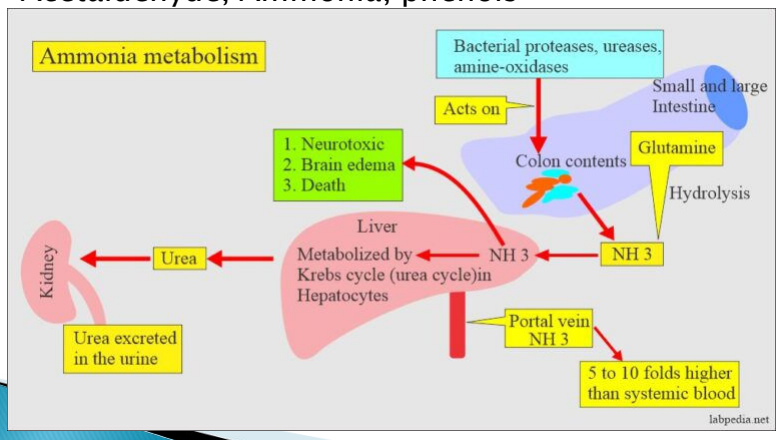
- SIBO = Elevated folate levels
- Bacteria in small intestine can impair methylation cycle by releasing too much folate
- Gut methylation SNPs of concern:
  - COMT -61 P199P, COMT V158M, MAOA A R297R

https://pubmed.ncbi.nlm.nih.gov/23853579/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3099351/

89

The Gut and Liver

- The liver is exposed to the metabolic products generated by the gut microbiome:
  - Acetaldehyde, Ammonia, phenols



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3418802/

90

Gut Polyphenol Production

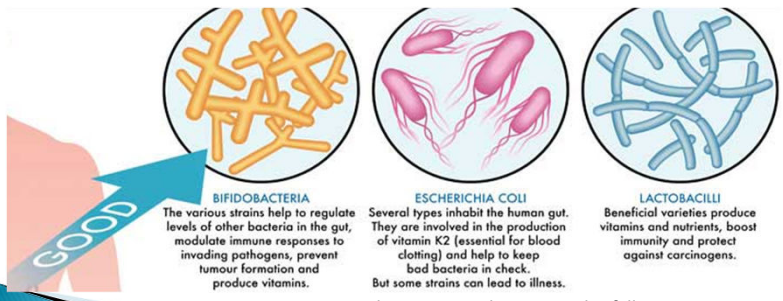
- Gut polyphenols interact with COMT and can inhibit COMT enzyme.
- We excrete 50-100mg of volatile phenols daily in the form of 4-cresol, phenol and 4-ethylphenol
- Cresols are attributed to Clostridium, Bifidobacterium and Bacteroides fragilis.
- E. coli is associated with phenol production.

https://pubmed.ncbi.nlm.nih.gov/22674330/
https://pubmed.ncbi.nlm.nih.gov/5432229/

91

Gut Bacteria

- Many Bifidobacteria are folate producers,
- While Lactobacilli are folate consumers.
- Gut dysbiosis can lead to hypo- or hypermethylation.



https://journals.asm.org/doi/full/10.1128/AEM.01763-06
https://doi.org/10.1016/S0168-1605(02)00170-8

92

Gut Microbiota as an Epigenetic Regulator

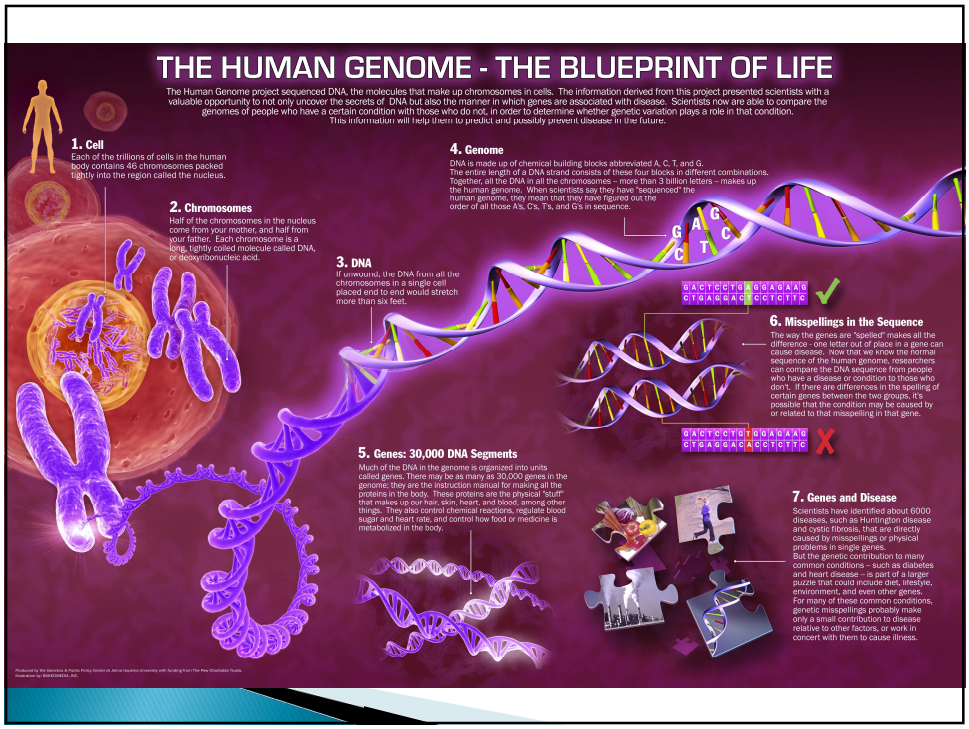
- Studies have shown that metabolites produced by beneficial bacteria serve as critical cofactors and regulators of epigenetic processes.
- One study "revealed a clear association between bacterial predominance and epigenetic profiles. The genes with differentially methylated promoters in the group in which Firmicutes was dominant were linked to risk of disease, predominantly to cardiovascular disease and specifically to lipid metabolism, obesity, and the inflammatory response."

https://journals.asm.org/doi/full/10.1128/mBio.02113-14

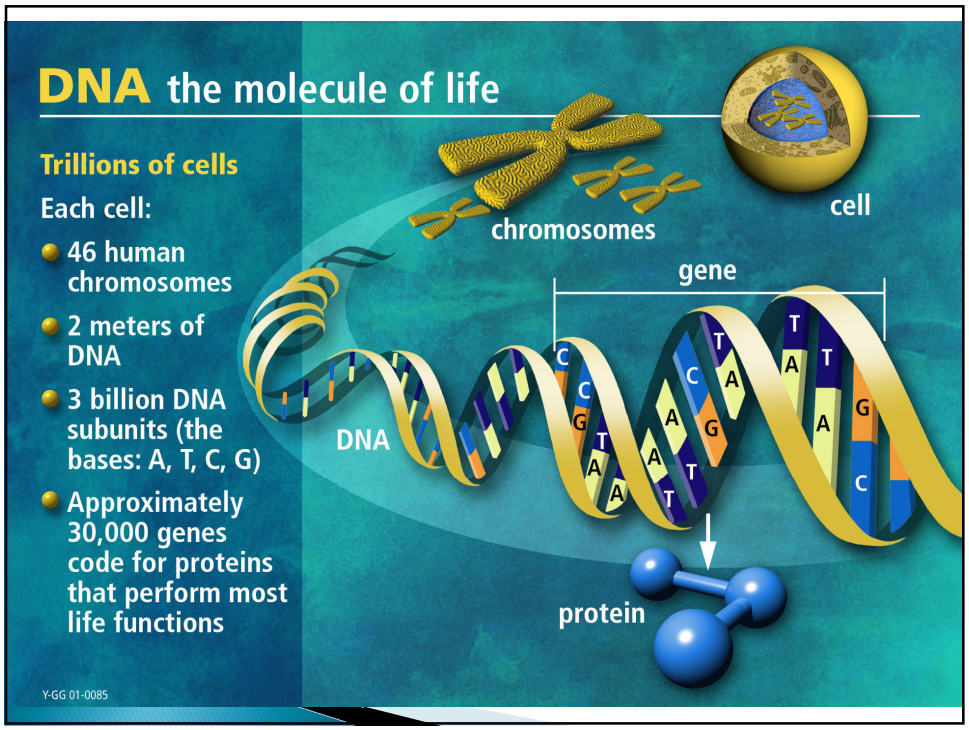
93

6) GENETIC POLYMORPHISMS

94


THE HUMAN GENOME - THE BLUEPRINT OF LIFE
The Human Genome project sequenced DNA, the molecules that make up chromosomes in cells. The information derived from this project presented scientists with a valuable opportunity to not only uncover the secrets of DNA but also the manner in which genes are associated with disease. Scientists now are able to compare the genomes of people who have a certain condition with those who do not, in order to determine whether genetic variation plays a role in that condition. This information will help them to predict and possibly prevent disease in the future.
1. Cell
Each of the trillions of cells in the human body contains 46 chromosomes packed tightly into the region called the nucleus.
2. Chromosomes
Half of the chromosomes in the nucleus come from your mother, and half from your father. Each chromosome is a long, tightly coiled molecule called DNA, or deoxyribonucleic acid.
3. DNA
If unwound, the DNA from all the chromosomes in a single cell placed end to end would stretch more than six feet.
4. Genome
DNA is made up of chemical building blocks abbreviated A, C, T, and G. The entire length of a DNA strand consists of these four blocks in different combinations. Together, all the DNA in all the chromosomes – more than 3 billion letters – makes up the human genome. When scientists say they have "sequenced" the human genome, they mean that they have figured out the order of all those A's, C's, T's, and G's in sequence.
5. Genes: 30,000 DNA Segments
Much of the DNA in the genome is organized into units called genes. There may be as many as 30,000 genes in the genome; they are the instruction manual for making all the proteins in the body. These proteins are the physical "stuff" that makes up our hair, skin, heart, and blood, among other things. They also control chemical reactions, regulate blood sugar and heart rate, and control how food or medicine is metabolized in the body.
6. Misspellings in the Sequence
The way the genes are "spelled" makes all the difference - one letter out of place in a gene can cause disease. Now that we know the normal sequence of the human genome, researchers can compare the DNA sequence from people who have a disease or condition to those who don't. If there are differences in the spelling of certain genes between the two groups, it's possible that the condition may be caused by or related to that misspelling in that gene.
7. Genes and Disease
Scientists have identified about 6000 diseases, such as Huntington disease and cystic fibrosis, that are directly caused by misspellings or physical problems in single genes.
But the genetic contribution to many common conditions – such as diabetes and heart disease – is part of a larger puzzle that could include diet, lifestyle, environment, and even other genes.
For many of these common conditions, genetic misspellings probably make only a small contribution to disease relative to other factors, or work in concert with them to cause illness.

95


DNA the molecule of life
Trillions of cells
Each cell:
46 human chromosomes
2 meters of DNA
3 billion DNA subunits (the bases: A, T, C, G)
Approximately 30,000 genes code for proteins that perform most life functions
chromosomes
cell
gene
DNA
protein
Y-GG 01-0085

96

Genetic polymorphisms (SNP's) CLINICAL RELEVANCE

BEN LYNCH ND:

- "The majority of SNPs have no effect on the body at all. None. They could be in regions of the gene that don't impact the genetic function at all. It doesn't affect the shape, it doesn't affect the reading of the gene, doesn't affect the switching on or off of the gene."
- "A lot of people will get their genetic report and they're like, "Oh I have all these SNPs!" The question is, "Is that particular SNP clinically relevant?" There is another clinically relevant SNP, like MTHFR…677 is very relevant."

97

What are SNPs?

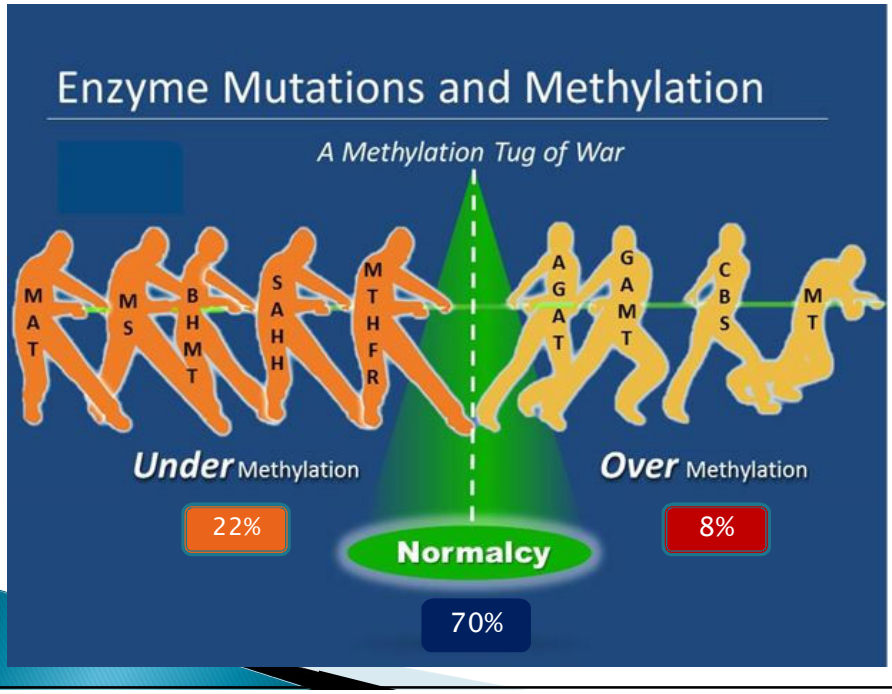
- SNP = "Single Nucleotide Polymorphism"
- They are the most common type of genetic variation among people.
- A SNP represents a difference in a single nucleotide, which is a DNA building block.
- Example: a SNP may replace the nucleotide cytosine (C) with the nucleotide thymine (T)

98

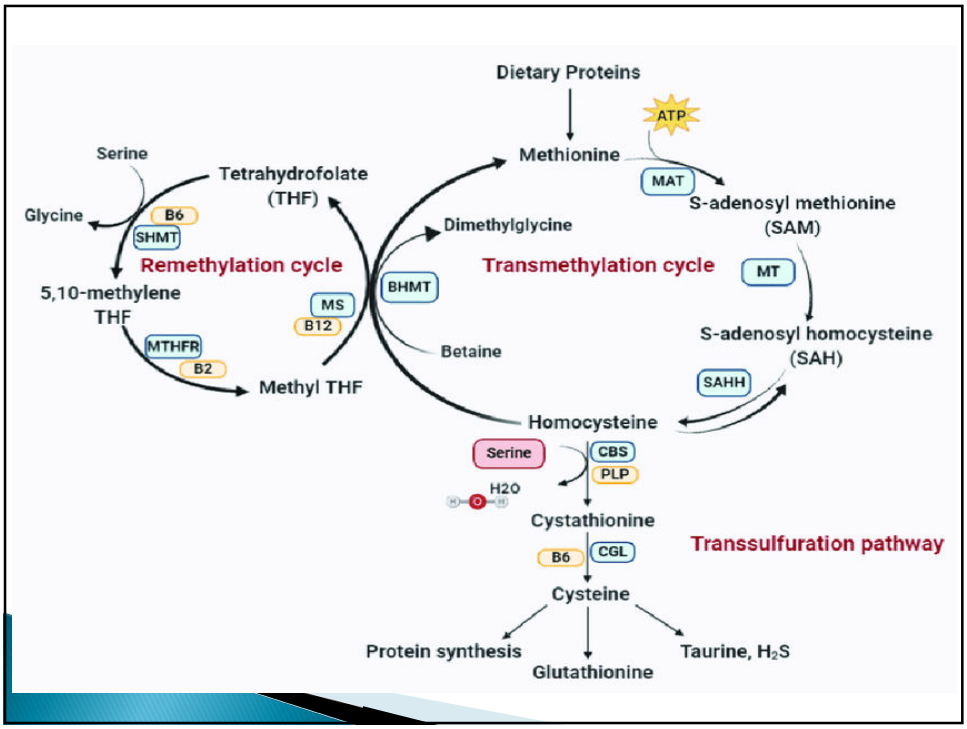
Genes are not the Whole Story!

- Genes do not tell us about the functional methylation capacity.
- A SNP may predispose someone to impaired methylation, but that does not mean they have impaired methylation.
- On the other hand, a person with no SNP may still need methylation support.

99



100



101

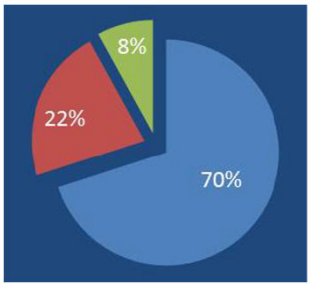
Methylation and Mental Health

- Methylation is a dominant factor in epigenetic processes that regulate neurotransmitter activity at serotonin and dopamine receptors.
- The methyl/folate ratio has a powerful impact on gene expression of reuptake transport proteins.
  - More than 60% of anxiety, depression, and psychosis patients exhibit a serious methylation imbalance.

102

2 Types of Methylation Disorders

UNDERmethylation OVERmethylation



Normal Methylation = 70%
UNDER Methylation = 22%
OVER Methylation = 8%

103

Incidence of UNDERmethylation

Autism-Spectrum	98%
Antisocial Personality Disorder	95%
Schizoaffective Disorder	90%
Oppositional-Defiance	85%
Anorexia	82%
Depression	38%

104

UNDERmethylation

CLINICAL
- HIGH histamine
- Whole Blood histamine >70
- LOW serotonin
- LOW dopamine
- LOW SAMe/SAH ratios
- Diagnosis of Autism, OCD, Antisocial Personality Disorder, Oppositional Defiant Disorder, Schizoaffective Disorder

SYMPTOMS / TRAITS
- Perfectionist
- Stubborn/Strong-willed
- Competitive
- OCD tendencies /Controlling behavior
- Calm demeanor but high inner tension
- Frequent headaches
- History of high accomplishment
- High fluidity (tears,saliva,etc)
- 75% have seasonal allergies
- High libido
- Good response to SSRIs

105

Primary causes of UNDERmethylation

1. Mutations (SNPs) in the Methylation Cycle...
   - MTHFR, MS, BHMT, MAT, SAHH, etc.
2. Histamine overload
   - Inverse relationship with methyl
   - HNMT enzyme breaks down histamine, and SAMe is a cofactor
3. Protein deficiency or Malabsorption

106

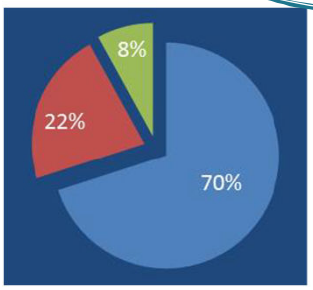
UNDERmethylators

- Tend to produce LOWER levels of the neurotransmitters serotonin, melatonin, dopamine, norepinephrine
- Associated with low energy, internal anxiety, depression and anxiety, but not always
- Tend to develop excess folate levels (need to monitor folic acid)
- When given supplements with methyl donors, they become more mentally alert

107

2 Types of Methylation Disorders

UNDERmethylation OVERmethylation



Normal Methylation = 70%
UNDER Methylation = 22%
OVER Methylation = 8%

108

Incidence of OVERmethylation

Panic/Anxiety Attacks	64%
Paranoid Schizophrenia	52%
ADHD	28%
Behavior Disorders	23%
Depression	18%

109

OVERmethylation

- CLINICAL
- LOW histamine
- Whole blood histamine <40
- HIGH norepinephrine
- HIGH serotonin
- HIGH dopamine
- Elevated SAMe/SAH ratios

- SYMPTOMS
- High anxiety / panic tendency
- Hyperactivity / nervous legs / pacing
- High pain threshold
- Low motivation
- Non-competitive
- Absence of seasonal allergies
- Food / chemical sensitivities
- Low libido
- Adverse reaction to SSRI's, antidepressants, SAMe, Methionine, anti-histamines

110

Primary causes of OVERmethylation

1. Impaired Creatine Synthesis
   - AGAT or GAMT SNPs
   - Arginine or Glycine Deficiency
2. Impaired Cystathionine Synthesis (CBS SNP)
3. Methyltransferase SNPs

111

OVERmethylators

- Tend to have ELEVATED serotonin, dopamine, norepinephrine
- Associated with hyperactivity, outwardly expressed anxiety, but not always
- Become hyper when given methyl donors

112

Lab Tests for Methylation Status*

1. SAMe / SAH Ratio (limited availability)
2. Whole blood histamine (methylation marker)

*Genetic tests such as MTHFR cannot determine the NET EFFECT of SNPs that affect methylation

113

MTHFR C677T and A1298C

- These are the 2 most well-studied and tested MTHFR mutations that affect the enzyme's function.
- (It is suspected that there are at least 30 different types of MTHFR mutations.)
- "Normal" genes: C677C, A1298A
- C677T mutation = change from cytosine (C) to thymine (T) at position 677 within the gene
- A1298C mutation = change from adenine (A) to C at position 1298 within the gene

114

Effects of C677T vs. A1298C

C677T mutation	A1298C mutation
1. Folate metabolism – inability to convert folate to methylfolate 2. Homocysteine elevated (cardiovascular issues) 3. Impaired methylation 4. Nutritional imbalances: problems utilizing nutrients (AA, EFAs, vitamins, minerals) 5. Reduced Detoxification	1. Neurotransmitter problems: mental health and behavioral issues 2. Nutritional imbalances: problems utilizing neurotransmitter producing amino acids and nutrients 3. Mild impairment of methylfolate production

115

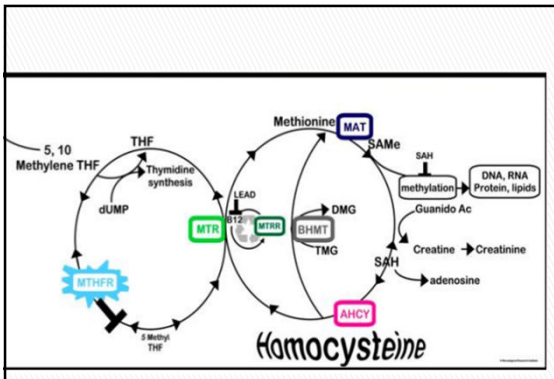
MTHFR C677T and A1298C

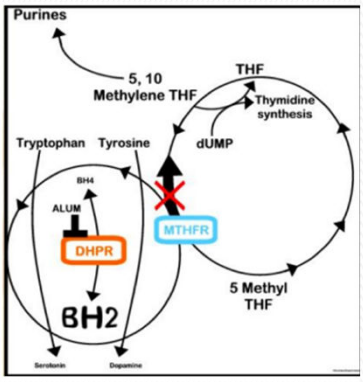
- C677T is found to be more problematic than A1298C

Genotype	677CC 2 normal 677s	6T7CT heterozygous one 677 variant	677TT homozygous two 677 variants
1298AA two normal 1298s	100% enzyme acitivity	66% enzyme acitivity	25% enzyme acitivity
1298AC heterozygous one 1298 variant	83% enzyme acitivity	48% enzyme acitivity	not analyzed
1298CC homozygous two 1298 variants	61% enzyme acitivity	not analyzed	not analyzed

Adapted from data presented by van der Put et.al.[3]
https://pubmed.ncbi.nlm.nih.gov/9545395/

116





5,10-Methylene-THF → 5-Methyl-THF

C677T

5-Methyl-THF + BH2 → 5,10-Methylene-THF+BH4

A1298C

117

MTHFR C677T and A1298C

- "Normal" = "wild type" = "Homozygous wild"
- Homozygous = same
- Heterozygous = different

Genetic Markers

VibrantAmerica

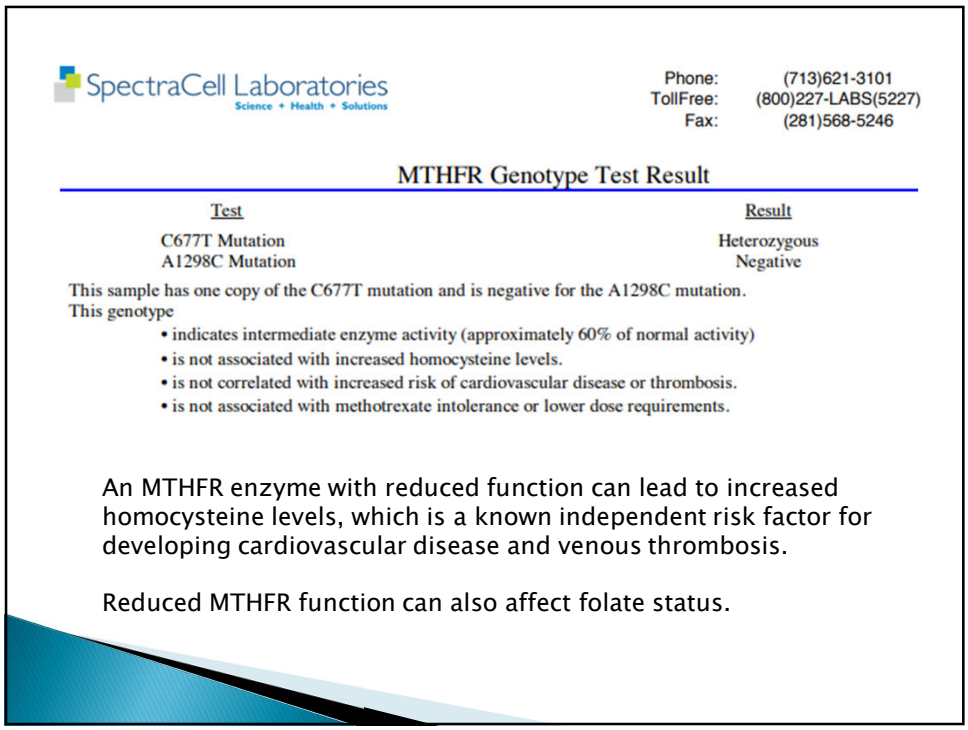
Vibrant America | 1021 Howard Ave, Ste B. San Carlos, CA 94070
1(866) 364-0963 | support@vibrant-america.com | www.vibrant- america.com

MTHFR

Assay	Result
MTHFR*	677C>T C/T; Heterozygous
	1298A>C A/C; Heterozygous

*Ex. One bad and one good copy at each base point.

118



SpectraCell Laboratories
Science + Health + Solutions

Phone: (713)621-3101
TollFree: (800)227-LABS(5227)
Fax: (281)568-5246

MTHFR Genotype Test Result

Test	Result
C677T Mutation	Heterozygous
A1298C Mutation	Negative

This sample has one copy of the C677T mutation and is negative for the A1298C mutation.
This genotype

- indicates intermediate enzyme activity (approximately 60% of normal activity)
- is not associated with increased homocysteine levels.
- is not correlated with increased risk of cardiovascular disease or thrombosis.
- is not associated with methotrexate intolerance or lower dose requirements.

An MTHFR enzyme with reduced function can lead to increased homocysteine levels, which is a known independent risk factor for developing cardiovascular disease and venous thrombosis.

Reduced MTHFR function can also affect folate status.

119

MTHFR

Tests	Results
C677T Mutation A1298C Mutation	Homozygous Negative

MTHFR Interpretation

This sample has two copies of the C677T mutation and is negative for the A1298C mutation.
* Is associated with decreased enzyme activity (approximately 30% of normal activity).
* Is associated with increased homocysteine levels.
* Is correlated with increased risk of cardiovascular disease or thrombosis.
* Is associated with potential methotrexate intolerance and patients may require dosage adjustments or discontinuation.

MTHFR Overview

MTHFR (methylenetetrahydrofolate reductase) is an enzyme involved in the metabolism of folate and homocysteine. It plays a role in maintaining cellular folate levels and is a cofactor needed to convert homocysteine (a potentially toxic amino acid) to methionine.

Certain common genetic point mutations have been characterized that reduce the function of the MTHFR enzyme. These are the C677T mutation (which is a change from cytosine to thymine at position 677 within the gene) and the A1298C mutation (which is a change from adenine to cytosine at position 1298 within the gene.) An MTHFR enzyme with reduced function can lead to elevated homocysteine levels, which is a known independent risk factor for development of cardiovascular disease and venous thrombosis. Reduced enzyme function can also affect folate status.

An additional area in which the function of MTHFR can have an effect is during methotrexate therapy. Methotrexate is a drug often used in treatment of certain cancers or autoimmune diseases. It is a structural analogue of folate and can interfere with folate metabolism. Defects in folate metabolism such as those potentially arising from mutations affecting MTHFR function can increase sensitivity to methotrexate and may lead to lower dosage requirements, increased side effects, or intolerance of the drug.

Testing Limitations

Only the C677T and A1298C mutations are analyzed in this assay. There may be other unknown non-genetic factors or genetic factors besides the tested mutations that can affect homocysteine levels, folate status, or drug sensitivities. Rare mutations in the primer binding sites used to detect the C677T and A1298C mutations may prevent detection. Specific dosing guidelines for methotrexate based on MTHFR genotype are not currently available.

MTHFR genotyping can provide useful information concerning risks of developing cardiovascular disease or thrombosis, or potential for increased sensitivity to methotrexate treatment. However, genotyping alone is not predictive of development of disease or complication and should not be used as the primary means of clinical diagnosis or treatment decision making. This information should be used by a physician in conjunction with additional clinical information to determine an appropriate treatment regimen.

120

The case of Autism

- Autism is a potentially preventable disorder!

1. 98% are found to be UNDERmethylating
2. 40% have impaired MTHFR functioning
3. Decreased glutathione levels
4. Research has shown children with autism have elevated antibodies to gluten proteins in wheat

121

Polymorphisms in the Methionine Cycle Pathway Methylenetetrahydrofolate Reductase (677C→T;1298A→C)

	Frequency	Odds Ratio	P Value
MTHFR677TT			
Control Individuals (183)	10.9%		
Autistic Children (231)	13.4%	1.26	.28
MTHFR677CT			
Control Individuals (183)	44.5%		
Autistic Children (231)	52.8%	1.4	.05
MTHFR677CT/1298AC			
Control Individuals (183)	18.1%		
Autistic Children (231)	26.4%	1.6	.03
MTHFRT Allele Frequency			
Control Individuals (183)	33%		
Autistic Children (231)	40%	1.33	.03

122

Transsulfuration Metabolites

	Control Children (n=33)	Autistic Children (n=20)		p value
Homocysteine (µmol/L)	6.4 ± 1.3	5.8 ± 1.0	↓	0.01
Cystathionine (µmol/L)	0.17 ± 0.05	0.14 ± 0.06	↓	0.002
Cysteine (µmol/L)	202 ± 17	163 ± 15	↓	0.001
Total glutathione (µmol/L)	7.6 ± 1.4	4.1 ± 0.5	↓	0.001
Oxidized Glutathione (nmol/L)	0.32 ± 0.1	0.55 ± 0.2	↓	0.001
GSH/GSSG Ratio	25.5 ± 8.9	8.6 ± 3.5	↓	0.001

123

C677T

- C677T mutations benefit from 5-MTHF supplementation
- NAC is the n-acetyl derivative of L-cysteine and plays a major role in hepatic gluthathione production. NAC downregulates glutamate activity. Studies show significant effects in the treatment of OCD and Autism.

(Psychopharmacology 2006. Jan 254-6); Reduction of self injurious behavior (J Clinical Psychiatry Nov 05,1494-97)

124

SNPs that can be affected by folate:

- Histamine (DAO, NAT, HNMT)
  - Genes that influence metabolism of histamine
  - These SNPs give a tendency to allergic reactions or hives
  - Folate may exacerbate the reaction
- Sulfur (SULT, SUOX, GSH)
  - Genes that influence glutathione production and how the body processes sulfur
  - Buildup of sulfur can cause headaches and flushes
  - Folate will create more sulfur

125

SNPs that can be affected by folate:

- Nitric Oxide (NO)
  - NO gene impairs the body's ability to process nitric oxide
  - Folate can result in too much uncoupled nitric oxide being created
  - B12 may help this issue

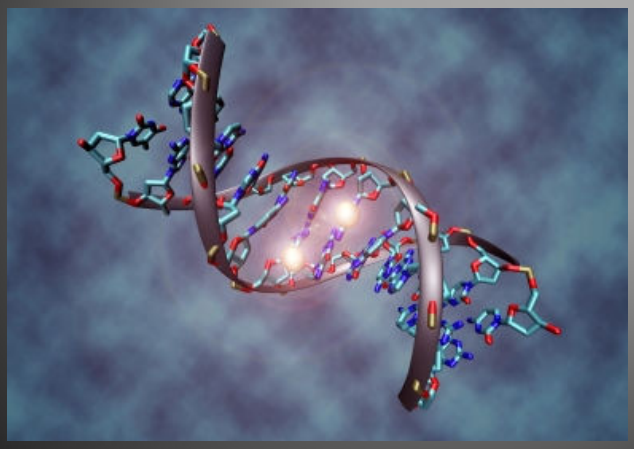
126

127

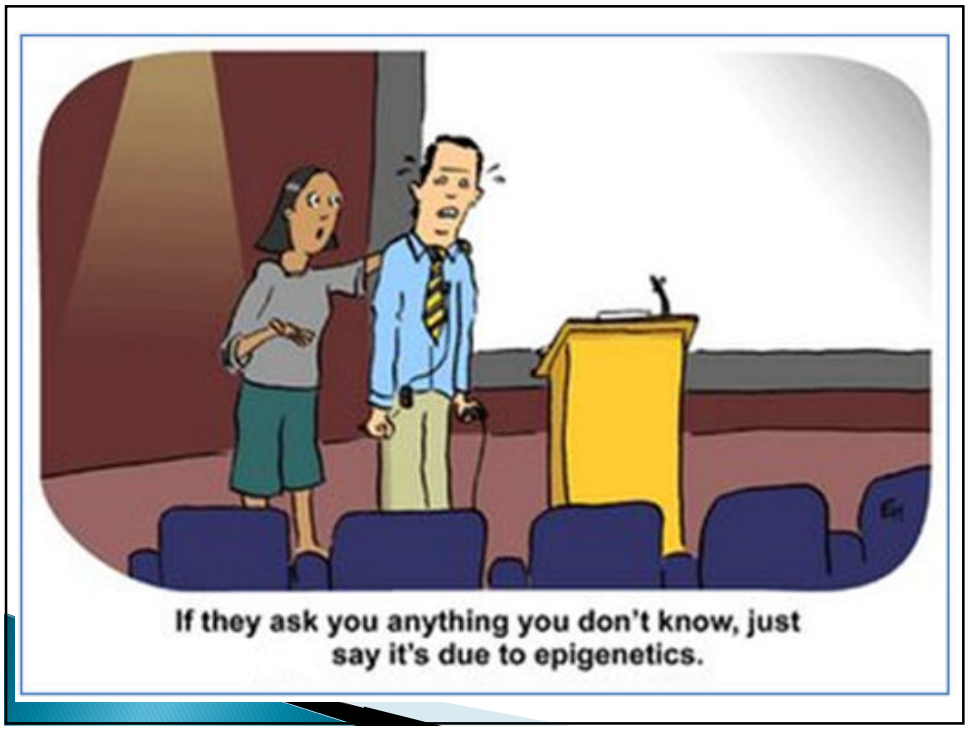
7) EPIGENETICS

128

Epigenetics and Methylation



129



130

Epigenetics and Methylation

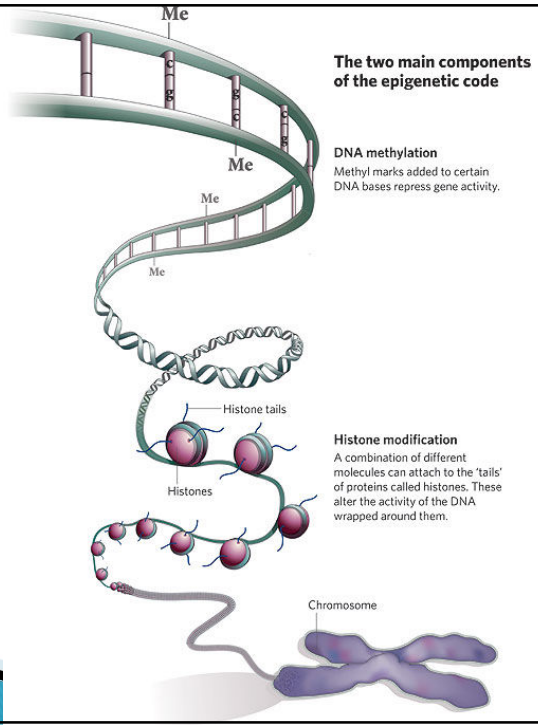
- There are 2 epigenetic processes:
  1. DNA Methylation
  2. Histone Modification

- DNA Methylation to enhance or inhibit gene expression happens in the womb before birth.
- Environmental factors at any age can alter this expression.

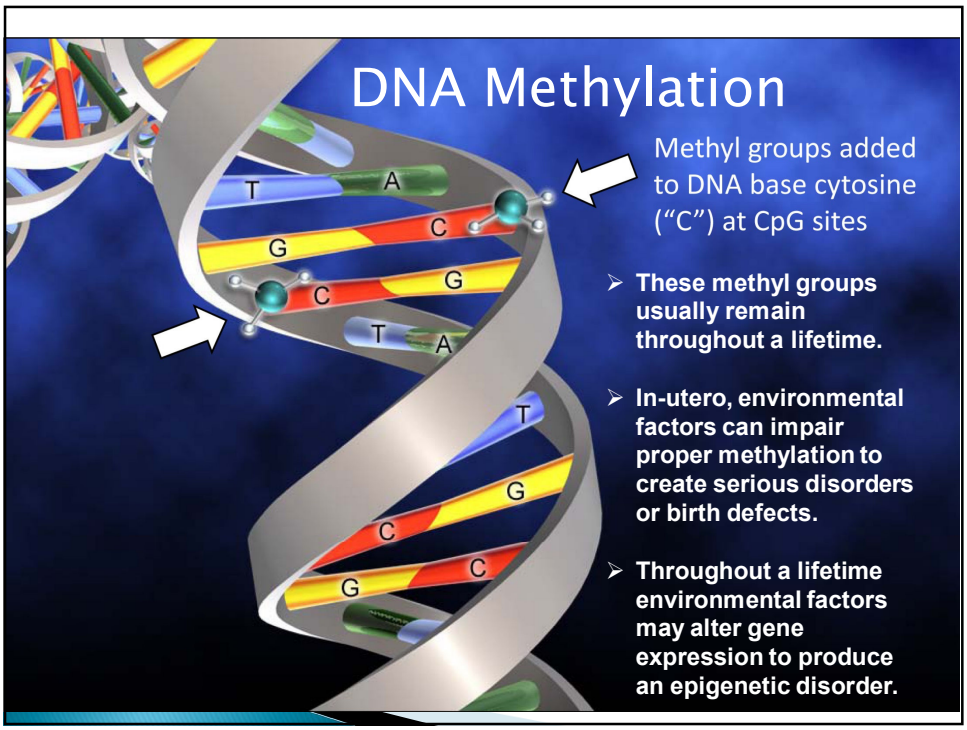
131

1.

2.



132

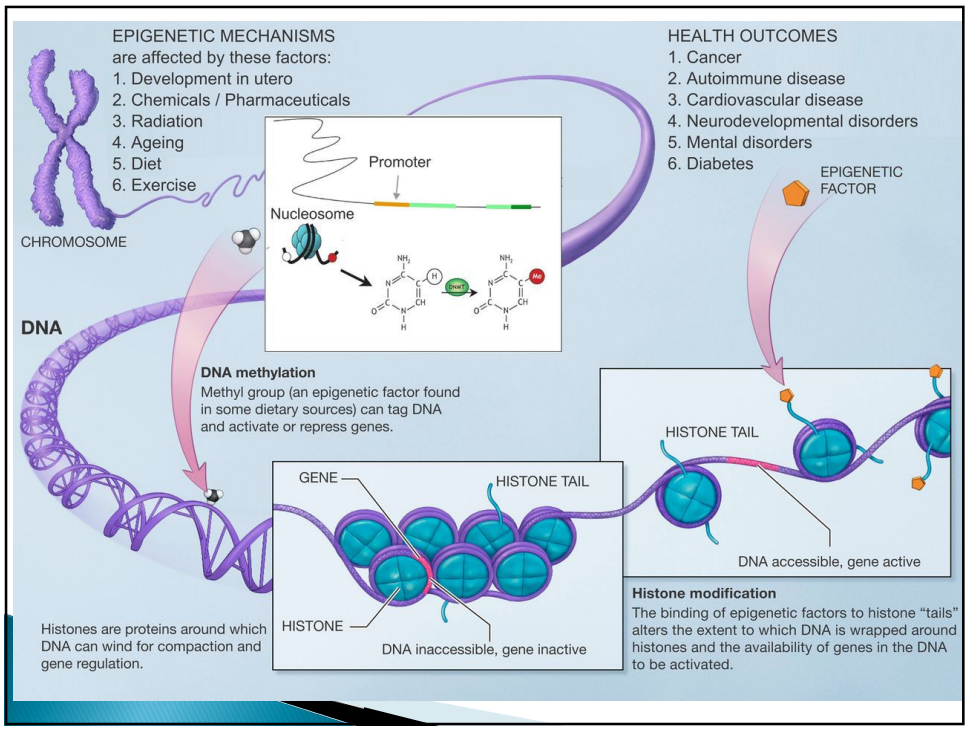


133

Histones

- Histones are support structures for fragile DNA
- They are composed of 8 linear proteins twisted together
- Histones inhibit or promote gene expression depending on chemical reactions at histone tails
  - Histone acetylation promotes gene expression
  - Histone methylation inhibits gene expression
- Nutrient therapies can modify histones by changing methyl/acetyl ratios

134



135

Histones

- DNA is a weak acid; Histones are strong bases.
- Acetylation decreases histone pH, which causes DNA to uncoil.
- Methylation increases histone pH, which increases DNA/histone coiling.
  - LOW methylation results in a preference for acetylation and therefore gene expression.
  - HIGH methylation inhibits gene expression.

136

Acetyl/methyl competition and Neurotransmitter activity

- Brain concentrations of serotonin and dopamine are less important than reuptake transport proteins.
- Reuptake transport proteins are the primary determinant of neurotransmitter activity at serotonin and dopamine receptors.
  - They remove neurotransmitters from the synapse.
  - They are formed by gene expression.
  - The total amount depends on acetyl/methyl competition at specific DNA regions.

137

Acetyl/methyl competition and Neurotransmitter activity

- Enzymes (acetylases, deacetylases, methylases, demethylases) are the dominant factor for attachment/removal of acetyl/methyl groups; not the concentration of acetyl/methyl groups.
- Epigenetic nutrient therapy to adjust serotonin or dopamine activity focuses on enzymes.

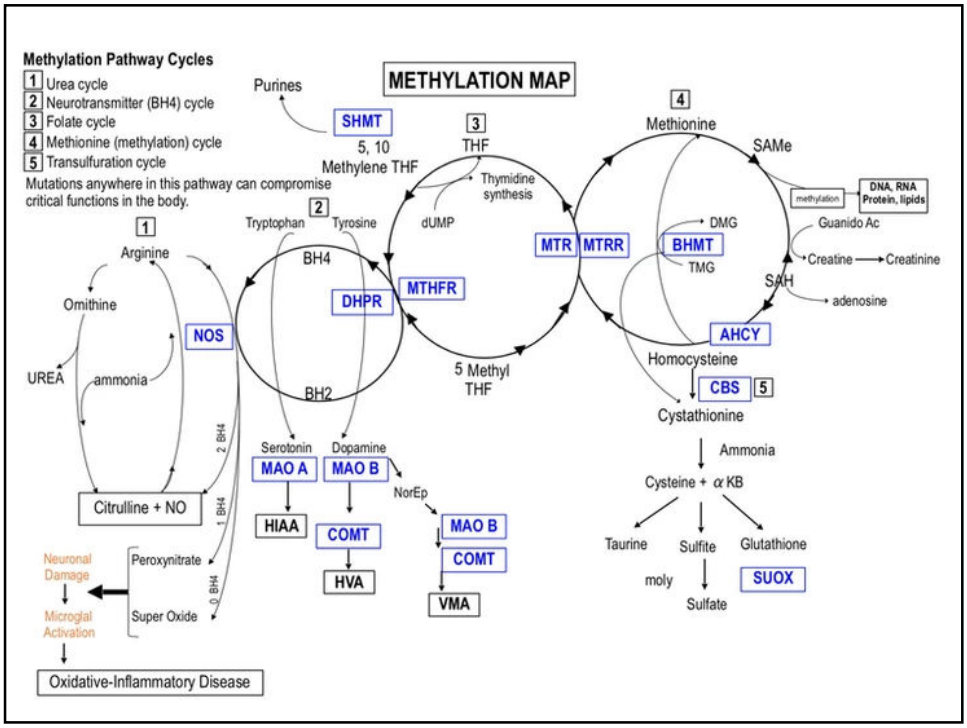
138

Bruce Ames research:

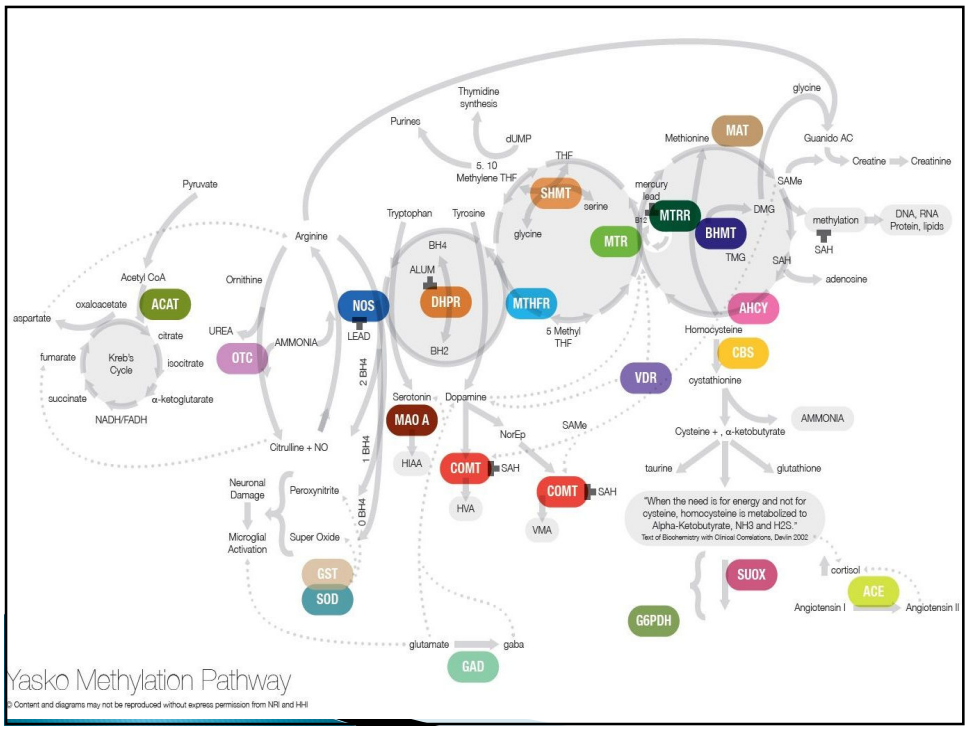
- Vitamins are converted to coenzymes, which together with enzymes, perform essential metabolic functions.
- About 50 diseases result from genetic mutations that reduce the ability of an enzyme to bind to its coenzyme.
- Ames found high-dose vitamin therapies overcome the mutations to normal reaction rate.
- Enzymes work better if they are flooded with cofactors.
- 22 diseases caused by defective binding to a B vitamin cofactor
- Of 3,870 known enzymes, 22% use cofactors
  - 112 of those utilize Vitamin B6

https://doi.org/10.1093/ajcn/75.4.616

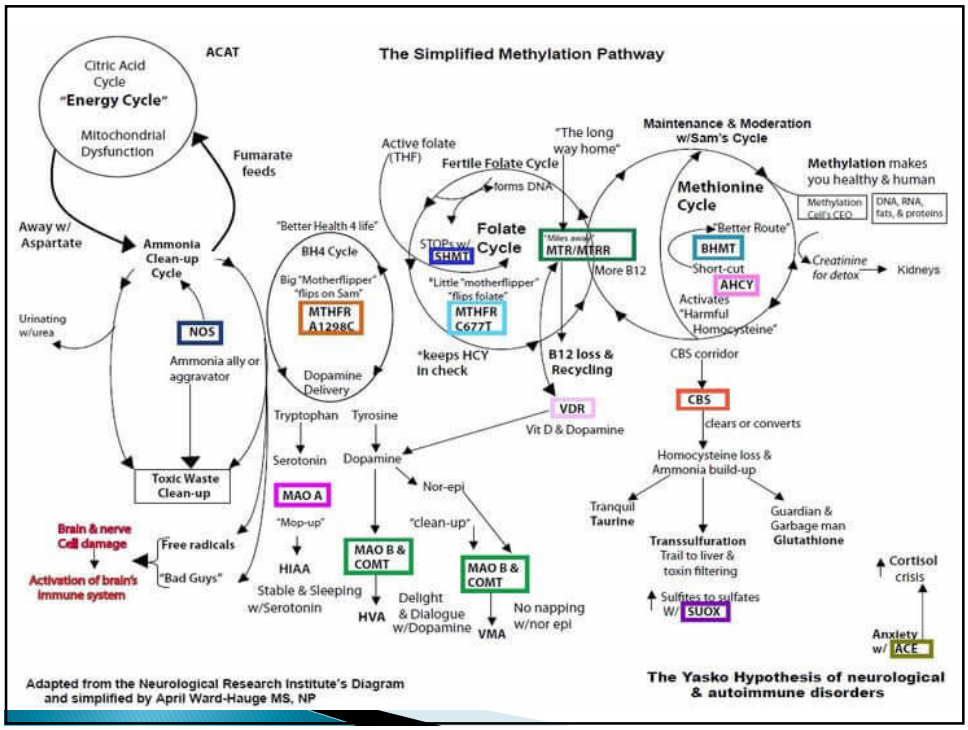
139



140


Thymidine synthesis
Purines
dUMP
5, 10 Methylene THF
THF
SHMT
serine
glycine
Tryptophan
Tyrosine
BH4
ALUM
DHPR
BH2
MTHFR
5 Methyl THF
MTR
Methionine
MAT
glycine
Guanido AC
Creatine
Creatinine
SAMe
DMG
TMG
SAH
adenosine
MTRR
BHMT
methylation
DNA, RNA Protein, lipids
Homocysteine
AHCY
CBS
cystathionine
VDR
Cysteine + , α-ketobutyrate
AMMONIA
taurine
glutathione
Pyruvate
Arginine
Acetyl CoA
Ornithine
aspartate
oxaloacetate
ACAT
citrate
UREA
OTC
AMMONIA
fumarate
Kreb's Cycle
isocitrate
succinate
α-ketoglutarate
NADH/FADH
NOS
LEAD
2 BH4
1 BH4
0 BH4
Citrulline + NO
Serotonin
Dopamine
MAO A
NorEp
SAMe
HIAA
COMT
SAH
HVA
VMA
Neuronal Damage
Peroxynitrite
Microglial Activation
Super Oxide
GST
SOD
"When the need is for energy and not for cysteine, homocysteine is metabolized to Alpha-Ketobutyrate, NH3 and H2S."
Text of Biochemistry with Clinical Correlations, Devlin 2002
SUOX
cortisol
ACE
Angiotensin I
Angiotensin II
G6PDH
glutamate
gaba
GAD
Yasko Methylation Pathway
© Content and diagrams may not be reproduced without express permission from NRI and HHI

141


ACAT
The Simplified Methylation Pathway
Citric Acid Cycle
"Energy Cycle"
Mitochondrial Dysfunction
Fumarate feeds
Away w/ Aspartate
Ammonia Clean-up Cycle
Urinating w/urea
NOS
Ammonia ally or aggravator
Toxic Waste Clean-up
Brain & nerve Cell damage
Free radicals
"Bad Guys"
Activation of brain's immune system
"Better Health 4 life"
BH4 Cycle
Big "Motherflipper" "flips on Sam"
MTHFR A1298C
Dopamine Delivery
Active folate (THF)
Fertile Folate Cycle
forms DNA
Folate Cycle
STOPs w/ SHMT
"Little "motherflipper" "flips folate"
MTHFR C677T
*keeps HCY in check
"The long way home"
MTR/MTRR
More B12
B12 loss & Recycling
VDR
Vit D & Dopamine
Tryptophan
Tyrosine
Serotonin
Dopamine
Nor-epi
MAO A
"Mop-up"
HIAA
Stable & Sleeping w/Serotonin
MAO B & COMT
HVA
"clean-up"
MAO B & COMT
VMA
Delight & Dialogue w/Dopamine
No napping w/nor epi
Maintenance & Moderation w/Sam's Cycle
Methionine Cycle
"Better Route"
BHMT
Short-cut
AHCY
Activates "Harmful Homocysteine"
Methylation makes you healthy & human
Methylation CoEs CEO
DNA, RNA, fats, & proteins
Creatinine for detox
Kidneys
CBS corridor
CBS
clears or converts
Homocysteine loss & Ammonia build-up
Tranquil Taurine
Transsulfuration Trail to liver & toxin filtering
Guardian & Garbage man Glutathione
Sulfites to sulfates W/ SUOX
Cortisol crisis
Anxiety w/ ACE
Adapted from the Neurological Research Institute's Diagram and simplified by April Ward-Hauge MS, NP
The Yasko Hypothesis of neurological & autoimmune disorders

142